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BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 21 1959

THE INCOMPUTABLE FACTOR IN CANCER PROGNOSIS*

BY

Sir GORDON GORDON-TAYLOR, K.B.E., C.B., F.R.C.S.

The subject I have chosen for this address is one of which I believe that Mitchell Banks might have expressed approval, since the special contribution to surgery for which posterity now justly acclaims him dealt with cancer and he repeatedly insisted on the necessity for appropriate surgery for this malady. To myself Mitchell Banks has long been a legendary figure of unusual interest, since in the exact moment of his arrival on the surgical stage and in the date of his first appeal, an appeal to be oft reiterated, for more radical surgery in cancer, especially in relation to mammary cancer, he stands intermediate between two Middlesex Hospital surgeons of former years. Charles Hewitt Moore (1821–70) became lecturer in anatomy and junior surgeon to the Middlesex Hospital at the phenomenally early age of 26. In 1867 Moore drew attention to the utter inadequacy of the operations that were being performed at that time for malignant disease. This epochal communication of Moore had the effect of determining Christopher Heath (1871, 1898), of University College Hospital, to remove the axillary glands when enlarged in breast cancer, but it was Banks (1878) who emphasized the importance and need of clearing the axilla, whether the glands were palpable or not.

Hard on the heels of Banks followed Alfred Pearce Gould (1882, 1892, 1910), whose private assistant I was for the nine years that preceded the outbreak of the 1914–18 war, who since 1880 had in his surgical practice embraced the tenets laid down by Banks in 1878 and who had reaffirmed them before the Medical Society of London in 1882. "A. P. G." throughout a long life of surgical teaching never failed, as I remember, to ascribe to Banks the credit of the extended operation for mammary cancer, including the systematic removal of the axillary glands in every case.

The stupidity and rank hostility of contemporaries, especially those in London, did not deter Banks from continuing on the course that he was convinced to be correct: but it required surgical propaganda, with all the glamour that inevitably arises from a transatlantic source, to convert those who had hitherto deliberately and obstinately closed their ears and eyes to the results of British endeavour. Gould, Heath, Jacobson, and Morris paid their tribute where tribute was really due.

William Mitchell Banks, born November 1, 1842, in the Scottish capital, and the son of a Writer to the Signet, received his education at the Edinburgh Academy and Edinburgh University. His M.D. thesis in 1864 on the Wolffian bodies remained for many years the recognized authority on this subject. Banks's researches in the field of embryology are the more remarkable since they were conducted a number of years before a reasonable microtome for serial sections was first described by His (1870).

He was fortunate in coming under the influence of great anatomists such as Goodsir and Turner in Edinburgh, and he was a demonstrator in the anatomical department of Allen Thomson in Glasgow in 1865 at a time when Lister was busy with his early researches in antiseptic surgery. Mitchell Banks had therefore an unrivalled anatomical background, which almost inevitably secured for him in turn the posts of demonstrator, lecturer, and finally professor of anatomy in the original Liverpool Infirmary School, which was to change its style and name in the years to come: it was only in 1894, when the Derby chair of anatomy was instituted in the University, that Banks resigned the professorship, and A. Melville Paterson succeeded him; he was made emeritus professor of anatomy. These were the days, as in my own case, when the avenue to the surgical staff of a hospital lay through the dissecting-room.

I have spoken of Banks's anatomical teachers, but in his address to the students of Yorkshire College, Leeds, in 1892 (Banks, 1893) he reveals his own humanity in the special tribute which he pays to Warburton Begbie, physician to the Edinburgh Infirmary in Banks's period there. He writes of Begbie thus: "I have always thought of him in my own mind as the Gentle Doctor and have always striven in the hospital ward, and in the clinical theatre, to imitate his example"; and again, "When he entered a ward, a new light seemed to shine in the faces of the sick. The very way in which he would put his hand on a patient's shoulder seemed to give the invalid comfort and strength."

Banks had the privilege in Edinburgh of being dresser and house-surgeon to James Syme, whom he speaks of as "the Napoleon of Surgery."

Sir Henry Morris, who sat next to Banks for several years in the Council Room of the Royal College of Surgeons of England, refers to him as an impressive and easy speaker, with a persuasive and pleasing manner, adding that there were three subjects on which Banks was very emphatic: (1) that Members of the College should not have votes for the Council; (2) that the number of physiologists in the Royal Society was unfairly in excess of the number of anatomists and of surgeons; and (3) that academic robes and ceremonial add to the dignity and impressiveness of official

*This is a slightly abridged version of the Mitchell Banks Lecture delivered at the University of Liverpool on October 29, 1958.

functions. He was responsible for the gown of the Fellows of the Royal College of Surgeons.*

The history of Mitchell Banks's achievement in the sphere of medical education, administration, and organization is scarcely germane to the subject of my lecture, but his worth was recognized by his election to the Council of the Royal College of Surgeons, and also as a representative on the General Medical Council. Mitchell Banks had interests outside surgery: he possessed expert knowledge of art, music, architecture, and archaeology; in one of his addresses he speaks of rowing in his younger years; Harrison refers to boxing in his memorial address; he also enjoyed mountain-climbing.

An Elusive Element

I have ventured to entitle this address "The Incomputable Factor in Cancer Prognosis" and desire to emphasize that elusive element, the unpredictable resistance of the individual to cancer invasion. *Tempora mutantur.* Time was when the competitive spirit in surgeons exhausted itself in vainglorious boastings of the removal of tumours remarkable for their pounds avoirdupois or huge cubic capacity: however, the day of colossal tumours in this country at least is past and gone. Surgical megalomania is now more happily satisfied by the recordings of unexpected, even unprecedented years of survival of patients after operation, radiotherapy, or hormonal or other form of treatment for malignant disease.

It is a matter of common knowledge that the prognosis in any case of cancer depends on certain factors: (*a*) perhaps most importantly, the histological grading of the tumour by an expert pathologist; (*b*) the stage of the new growth, especially the infiltration of surrounding parts, including neighbouring veins; (*c*) the invasion of lymphatic nodes; (*d*) the presence of metastases; (*e*) the appropriate method of treatment; and (*f*) the patient's own resisting power to cancerous invasion.

The importance of this last-named factor seems to be emphasized the more in view of the recent remarkable discoveries of Warren Cole and his co-workers (Cole *et al.*, 1958; Roberts *et al.*, 1958) concerning early invasion of the blood stream by cancer cells, and by the reflection that, despite these ominous findings, post-operative survival may often be indeed quite protracted.†

The proverbial *varium et mutabile* often ungraciously applied to the feminine counterpart of *homo sapiens* is not inapplicable to the behaviour of a cancerous growth. There are many modes of behaviour in a malignant tumour: it may proceed relentlessly to its ending; it may run a hurricane course; it may linger on for many years and may not even be the final cause of death of the patient, its protracted course betokening its low malignity, the vigorous resisting power of the patient, or the interplay of these two factors.

On the other hand a tumour which is growing strongly may have the metabolic balance turned against it by some metabolic alteration of the parent organism and may cease growing for a variable time and even become smaller, only to assume its proliferative activity again at a later period. Some of us have observed new growths disappearing completely, so that the patient is apparently cured. This phenomenon has been observed in secondary as well as in primary growths.

Latent Carcinoma

The "latent carcinomata" appear also to attest this *vis medicatrix naturae*, and those unknown forces which can keep cancer cells dormant in the vicinity of the exsected primary tumour or in the lymph nodes or distant anatomical regions for a mammoth number of years before their resurgence point to a great auxiliary defensive power resident in the host in some cases.

In the matter of latent carcinoma of the prostate, to which Franks (1954, 1956a, 1956b) especially has drawn attention, these tumours possess all the morphological structure of carcinoma and some biological characteristics, including infiltration of capsule, blood vessels, and lymphatics and, exceptionally, infection of lymphatic nodes. Nevertheless these tumours have not occasioned the patients any serious harm and were certainly not the cause of their death. Raeburn and Spencer (1953) found latent carcinomata in the lungs, while Nicholson (1923), Newcomb (1936), Trinkle (1936), and Willis (1953) have described latent carcinoma of the kidney.

Unsuspected carcinoma in surgically removed goitres, often invading blood vessels, has of course frequently been reported, and it is well known that carcinoma of the thyroid may remain latent and only reveal itself by the development of metastases in bone, lung, or liver.

Small cortical nodules may be found in the adrenal; such may recur locally after removal or may metastasize. Even in the gastro-intestinal tract latent carcinomata have been demonstrated.

In some cases, especially in the prostate, the cause of latency may be hormonal environment; this suggestion is a laudable effort to explain "the resisting power of the host" in the light of recent researches.

Hadfield (1954) pointed out that when the interval between the excision of some primary malignant tumour and the appearance of secondaries exceeds say, 2, and reaches 4, 14, or 40 years, it is difficult to believe that cellular proliferation in the residual tumour has been continuous, and it seems almost impossible to escape the conclusion that the cells of the dormant growth have been in a state of temporary mitotic arrest. Such a conclusion becomes all the more irresistible when we observe sometimes the marked resurgence of clinical activity in these long-dormant growths after years of latency. When we can only faintly adumbrate the causal agencies determining the growth, regression, and even the disappearance of tumours, still less do we know the environmental factors required to induce mitotic arrest for from 3 to 30 years.

Dormant cancer cells are prone to lurk (*a*) in or near the site of the original operation; (*b*) in regional lymph nodes; (*c*) in deeply placed organs. Such foci must have been implanted before or during the excision

*A special gown for Fellows was authorized by the Council on May 12, 1898, after a motion to that effect by Mr. Mitchell Banks. The design of the gown, very much as it is now, was authorized at the subsequent meeting of the Council. Banks had retired from the Council before a gown for Members was authorized at the end of 1899. The Hunterian Professor's gown, which had been in use for some time, appears to have been the model for the Fellows' gown.

†According to Warren Cole and his associates cancer cells can be demonstrated in the circulating blood in a considerable percentage of cancer patients, even at a relatively early stage of the malady. In Warren Cole's and in Engell's (1955) series a positive finding was found even in the peripheral blood in upwards of 10% of "curable" patients. Clumps of cells are more likely to be found in blood taken from a vein draining the tumour area, and there is often an increase in the number of cancer cells in the circulating blood during the manipulations incident to the removal of the tumour, and in certain cases examined the cancer cells disappear from the circulating blood within a few minutes of the removal of the primary tumour. These results have been confirmed in D. H. Patey's unit at Middlesex Hospital.

of the primary neoplasm. In at least 50% of cases of malignant disease recurring after latent periods varying from 5 to 30 years the reactivated metastases are found in the haemopoietic bone marrow. Clifton and his co-workers (1952) especially have emphasized this proclivity of the bone marrow to invasion by cancer cells which may lie dormant for a long time; they state that in 33% of cases of carcinoma of the prostate cancer cells were demonstrated in the sternal bone marrow and in the ilium, and that in 9% there was widespread skeletal dissemination of growth with no diagnostic evidence other than that provided by the marrow biopsy. The haemopoietic system, the hypophysis, and the adrenal appear to be especially vulnerable to this early invasion.

Kettle (1912) drew attention to the existence of microscopic foci of metastatic carcinoma in the normal-sized spleen, and suggested that such growths lying in the territory drained by the portal vein might be the source of hepatic metastases when the primary growth lay outside the portal vein drainage area.

Carcinoma of the Breast

The protracted period during which mitotic activity may be arrested and to which Hadfield (1954) referred is well exemplified in some cases of cancer of the breast. One of my own patients who had been operated on by me for carcinoma of the breast 36 years before was alleged to have died of an "abdominal recurrence"; however, no histological evidence was forthcoming, and the verdict of this exceptionally late recurrence must remain "not proven."

On the other hand, one of Bryant's (1902) cases of cancer of the breast did recur in a woman of 82, 32 years after her initial operation, while another of his patients, aged 77, developed a recurrence over the sternum 31 years after the first operation for mammary cancer. She was alive five years later—that is, 36 years after the original operation.

Still another case reported by Bryant concerned a woman of 63 who developed a recurrence in the scar 25 years after the removal of a mammary tumour. She was alive five years later—that is, 30 years after the original operation.

In a case of recurrent carcinoma of the breast recorded by Steward (1925) with praiseworthy accuracy the patient had had her left breast removed by Butlin 31 years previously, and when seen by Steward was 81 years of age. A few months before Steward was consulted her general practitioner had discovered three small hard nodules beneath the skin in the immediate vicinity of the operation scar: these had slowly enlarged. Steward found them to be each half an inch (1.3 cm.) in diameter, each one separated from the other two by about one and a half inches (3.8 cm.): they were not attached to the skin, or apparently to the deeper structures. During the previous two months there had been some enlargement of the veins on the front of the chest, and there was some degree of breathlessness.

Whether the disease recurred at four separate spots at the same moment or whether the subcutaneous nodules were efflorescences from a mediastinal recurrence is immaterial, but the fact remains that cancer cells had lain dormant for 31 years.

Verneuil (1888) dealt with a recurrence in a woman 30 years after her first operation for a mammary tumour; and I myself saw in consultation an abdominal tumour subsequently reported as a "spheroidal-celled carcinoma of mammary type"; the breast had been removed by the late Sir Cuthbert Wallace 30 years before.

Bowlby's (1925) case of recurrence 24 years after the surgical removal of a mammary tumour by Sir Thomas Smith showed itself as a small lump two inches (5 cm.) below the middle of the right clavicle; there was also a hard gland above the clavicle. Examination under anaesthesia revealed that the recurrent malady had already spread more widely, and the patient died within a year with visceral dissemination and infected cervical glands.

About a quarter of a century ago I saw within a very brief space of time three cases of recurrence in the scar of a previous radical mastectomy performed by sundry other surgeons, respectively, 21, 22, and 23 years previously, and only recently (October, 1958) I was informed of a small recurrence in the scar of a radical mastectomy performed by me 21 years ago.

It becomes difficult to ignore the pronouncement of Mitchell Banks in his Lettsomian Lectures of 1900 that no matter how early the case of cancer or how thorough the treatment no patient is free from the possibility of recurrence until death ensues from some other cause.

Causal Factors in Recurrence

In the preceding paragraphs I have been especially referring to recurrence in breast cancer, and in some cases no causal factor save possibly advancing age can be impugned as standing in any relationship to the recrudescence of the malady, but in others recurrence does appear to have been preceded by intercurrent disease or by surgical operation for some independent condition.

In one of my patients a recurrence in the scar of a previous radical mastectomy developed 17 years later—a few weeks after a very severe attack of acute pyelonephritis for which I had seen the patient, the previous operation area at that time being completely sound. The reactivated malady ran a hurricane course, and in a month or two the patient was dead.

In another case of my own an attack of "shingles" seemed to determine recurrence of the malady 12 years after the initial surgery; in still another case recurrence in the scar followed quickly on a haemorrhoidectomy performed 16 years after the breast operation.

Thrice I have seen recurrence follow an operation for an independent condition—for example, gall-stones—and once after a herniotomy performed under local anaesthesia for an irreducible inguinal hernia.

In these cases cancer resistance or cancer immunity long maintained appears to have been broken down by happenings unconnected with the original malady.

Certain tables set forth in previous communications (Gordon-Taylor, 1938, 1948) of mine dealing with prognosis in mammary cancer emphasize the not inconsiderable percentage of patients that may be expected to survive 10 years according to the stage of the disease (and the histological grading) when the patient comes under treatment. It would have been fascinating to ascertain the ultimate fate of upwards of 150 patients with cancer of the breast who in 1938 had survived 10 years since their operation, but the destruction by enemy air activity in 1941 of case records and tables of cases carefully worked out has effectively

precluded this; nevertheless certain cases of long survival remain indelibly impressed on the palimpsests of memory.

In particular, I would mention the case of a woman, now an octogenarian, operated on 47 years ago, in whom at the time of the operation there were already one or two infected glands in the axilla. Ever since the time of her operation she has been cursed by oedema of her arm when she performs much in the way of exercise; but there has been no recurrence of her malady.

Another patient, operated on in July, 1914, for a carcinoma of the breast without involvement of the axillary glands, has remained free from recurrence more than 44 years. Still another patient who had a preliminary biopsy and a radical operation a few days later on account of the sinister histological report survived 36 years and unfortunately met with a fatal road accident. Another is alive and free from recurrence 35 years after a radical operation.

Two patients with carcinoma of the breast came under my care in 1925 and in 1931 respectively, in whom at operation the axilla was found to be literally stuffed with infected glands. The earlier case I have lost sight of since the outbreak of the 1939–45 war, but she certainly survived 14 years. The later case I frequently saw; this patient was a few days short of 90 when she recently died suddenly free from recurrence, nearly 28 years after what seemed an ill-omened start.

Cancer of the Tongue

Cade and Lee (1957), in their excellent contribution on cancer of the tongue, refer to reactivation of the disease after many years of apparent "cure"; they quote cases recurring at 5, 6, 8, 10, and even 16 years after treatment, and mention Juliette Baud as having observed a recurrence as long as 21 years after previous successful radiotherapy.

A patient was admitted to the Middlesex Hospital under my care about 30 years ago with severe haemorrhage from a huge carcinomatous ulcer of the tongue, for which Holmes Sellors, at that time my registrar, ligatured the external carotid artery. Four days later a total glossectomy was performed, the alveolar portion of the lower jaw on the affected side being removed with the tongue. The man was seen periodically for 21 years, when he presented himself with a growth of the palate, which was inoperable. In view of the very extensive character of the growth 21 years before, and the deep infiltration of the palatine neoplasm I was inclined to regard this as a late recurrence rather than a separate primary growth.

A man was admitted under my care in 1923 with a huge carcinoma of the tongue involving the lower jaw. A total glossectomy along with removal of half the jaw was followed by freedom from recurrence for 24 years, the man dying from natural causes.

A man was operated on at his home in the wilds of the country: hemiglossectomy was performed by diathermy excision in 1926, followed by an elective block-dissection of the neck. The patient remained well for 15 years, dying in 1941 aged 78 from prostatic breakdown for which he obstinately refused to submit to surgery.

Perhaps the longest survival of a patient with cancer of the tongue is that reported by Manson (1922), of Warrington, who published a case of cancer of the tongue excised in 1888. The patient remained well until 1922, when he developed a carcinoma of the cardia, 34 years after the surgical removal of the lingual epithelioma.

Cancer of Cheek and Lip

Cancer of Cheek.—A distinguished patient had a considerable carcinoma of the buccal aspect of the cheek, which was first treated by teleradium, but recurrence took place; radium needles were then inserted. This appeared to "flare" the growth; a wide excision of the cheek was performed, including a portion of the alveolar process of the maxilla and of the mandible. The whole defect was left open, and the gap subsequently repaired by a plastic by Professor T. P. Kilner. More than 22 years later the patient died from causes unconnected with the original malady.

Basal-celled Carcinoma of Lower Lip involving Mandible.—G.L., in 1925, had a local excision of an ulcer and minor plastic repair. A recurrence which took place 10 months later was treated by diathermy; in 1928 the ulcer, which had recurred and was now attached to the bone, was submitted to radium treatment. In July, 1929, the malignant ulcer was treated by further radium. In March, 1930, further recurrence necessitated the removal of the whole of the lower lip, much of the mandible, and part of the left cheek and left upper lip. By July, 1932, plastic repair by Sir Harold Gillies of soft tissues for lip and chin was complete, and in November, 1933, a bone graft from the ilium was inserted. In 1958 the patient was sound and well nearly *29 years* after the radical operation.

Carcinoma of Lower Lip involving Mandible.—Miss H.P. in 1917 received some *x*-ray treatment abroad for excess of hair on her chin and face. In 1920 she was given snow treatment and in 1921 diathermy, by which time an ulcer was present on the chin. In 1937 she underwent the removal of some portion of her lip and bone and many plastic operations in Berlin, where the condition had not been considered malignant. In 1939 the stark malignancy of the condition demanded a wide excision of the whole area, including almost all the mandible. The degree of mutilation necessitated a temporary gastrostomy for feeding purposes. By the end of 1940 soft-tissue plastics by Sir Harold Gillies had proceeded far enough to allow the patient to swallow and the gastrostomy to close. Many bone grafts failed, but ultimately, in March, 1948, there was produced a solid bony arch, which could support her tongue and enabled her to wear a denture.* She died from an independent condition 11 years after operation.

Carcinoma of Hypopharynx and Oesophagus

Hypopharynx.—Several early cases of cancer of the hypopharynx treated by lateral pharyngotomy have survived upwards of five years before recurrence took place. One case, the sister-in-law of a distinguished general, survived 24 years without recurrence, and died only a year or two ago.

Oesophagus.—Only one case of mine of cancer of the thoracic oesophagus survived five years: this man died, without recurrence, from perforation of a peptic ulcer at the junction of the presternal skin-lined tube with his stomach. On the other hand, one case of cancer of the

*The above two cases were shown at the Clinical Section of the Royal Society of Medicine with four others on November 12, 1948, by Sir Harold Gillies (1949), to illustrate team surgery in cancer.

cervical oesophagus where a segment of the gullet was replaced by a cutaneous plastic survived 20 years.

Fibrosarcoma of Stomach, Spleen, and Splenic Flexure of Colon

At an operation performed in December, 1927, under paravertebral anaesthesia, supplemented by "splanchnic block," a fibrosarcoma of the stomach implicating the spleen and splenic flexure of the colon was removed. Five or six years later the patient became pregnant: the pregnancy was deliberately terminated by a hysterotomy, yet the patient developed a recurrence in the original upper abdominal scar. The recurrence was dealt with radically and the patient remained well for a number of years. Recurrences in the abdominal scar took place at intervals. Since 1952 I have lost sight of her, but she had survived my first operation 25 years.

Carcinoma of Body of Pancreas

A middle-aged man was operated on in July, 1927, for a cancer of the body of the pancreas; the tumour was about the size of the closed fist; it was removed, only a portion of the head of the pancreas in the concavity of the duodenum remaining. A length of splenic artery and splenic vein were removed with the tumour: the spleen was not ablated. The tumour was reported as a columnar-celled carcinoma: a lymphatic gland attached to the mass was not infected. The patient remained in excellent health for 11 years, when his general health began to deteriorate and a recurrence took place in the scar and was found on exploration to extend down to the vicinity of the previous area of ablation.

Carcinoma of Large Intestine

Cancer of the right-sided colon; carcinoma of caecum and ascending colon, implicating the abdominal wall: resection. Five years later, primary carcinoma of stomach: resection. Death one year later.—A married woman aged 45 had been under treatment at a private institution which exploited a fruit diet as a panacea for all ills. Unfortunately an extensive carcinoma of the right-sided colon was found to be present, which implicated the lateral abdominal wall; a portion of the abdominal parietes was included in the resection. Five years later the patient developed a carcinoma of the stomach, which was removed. Death followed from recurrence of the gastric cancer just over a year later, but there was no return of the cancer of the large bowel despite its initial extent.

Carcinoma of the hepatic flexure, involving lateral abdominal wall and liver.—A man aged 48 underwent in February, 1930, an excision of the right-sided colon, which had implicated the abdominal wall and the right lobe of the liver. About one-fifth of the liver was removed, including the gall-bladder. The patient died *seven years* later, doubtless from recurrence.

Primary carcinoma multiplex. Carcinoma of the right-sided colon involving the stomach: colectomy and partial gastrectomy. Nine years later, carcinoma of sigmoid involving bladder: resection. Three years later, Wertheim's hysterectomy for carcinoma of the cervix. Finally carcinoma of the bronchus, 19 years after her first operation.—A stout Jewess, aged 45, was operated on in the beginning of 1930. A new growth of a short right-sided colon was found to involve the pyloric end of the stomach. At the first operation, which was determined by symptoms of intestinal obstruction, the mass was completely excluded, the appropriate anastomoses being effected between the proximal segment of the stomach and jejunum and between the ileum and the transverse colon. A few days later the mass was exsected: a pathological fistula had traversed the growth from caecum to transverse colon. Almost 10 years later the patient then returned under my care with a carcinoma of the sigmoid. The tumour was removed by the Paul–Mikulicz procedure, the invasion of the fundus of the bladder necessitating removal of the upper part of this organ along with the colonic neoplasm. Some four years later Mr. Victor Bonney performed a Wertheim hysterectomy for a carcinoma of the cervix. Finally, in 1947 she reappeared with an obviously malignant gland in the left supraclavicular fossa, which proved to be secondary to a bronchial carcinoma, and the latter malady brought this story of recurrent cancer to its close.

A major aged 64 was operated on for a carcinoma of the caecum implicating a coil of small intestine remote from the ileo-caecal junction. Resection of right-sided colon and separate enterectomy of ileum were carried out. The patient remained well for nearly six years, and then developed a metastasis in the liver from which he died.

Cancer of left-sided colon and rectum. A 34-year survival after resection of a sigmoid growth.—A carcinoma of the colon occurred in a woman aged 56, for whom I performed a resection in 1924, very dissatisfied at the time with the limited amount of bowel below the tumour that I could take away in order to restore its continuity by an end-to-end anastomosis. The patient survived operation for almost 34 years, and died of causes unconnected with the primary malady.

There have been other survivals of long duration in cases with cancer of the left colon.

Carcinoma of sigmoid implicating the left tube and ovary. Resection: patient alive and well 27½ years later.—A married woman aged 56 was operated on for large-bowel obstruction on April 4, 1931. A sigmoid growth implicating the left ovary and tube was treated by a Paul–Mikulicz type of resection. The patient remained well nearly 28 years later.

Carcinoma of sigmoid implicating the abdominal wall, and left tube and ovary.—A married woman aged 60 was operated on for acute intestinal obstruction; a blind caecostomy was performed. Subsequently a malignant mass appeared, which comprised pelvic colon and left tube. The patient survived 20 years.

A 19-year survival after resection of a sigmoid growth.—A naval officer was operated on in October, 1939, for a sigmoid growth which produced acute intestinal obstruction. An exteriorization-resection method was employed. The patient remains in excellent health, more than 19 years later.

Carcinoma of the pelvic colon implicating abdominal wall, uterus, and left adnexa.—A married woman aged 55 was operated on in 1927 for acute intestinal obstruction. Laparotomy revealed a cancer of the pelvic colon: the abdominal incision was closed and a caecostomy performed. Subsequently the colonic growth was removed with a portion of the abdominal wall, the body of the uterus, and the left tube and ovary. The patient remained well till 1939—12 years—but has been lost sight of.

Carcinoma of pelvic colon, involving the abdominal wall, two coils of small intestine, and fundus of urinary bladder.—This patient *survived 10 years*, but has been lost sight of since the war.

A man aged 60, from whom a large abdominal mass was removed, involving the pelvic colon and many segments of small bowel. The abdominal muscles were quite considerably involved, and there was a large infected lymphatic gland. The man was alive and well eight years later.

Carcinoma of Rectum

Sister M., aged 48, a nun from a London convent, was referred to me at the end of 1929 for a huge ulcerating carcinoma of the rectal ampulla which had involved a considerable extent of the posterior vaginal wall and had perforated the posterior vaginal fornix. The vulva and perineum were constantly bathed in an offensive sanguineous and purulent discharge which leaked from the bowel and the genital passage: any attempt to remove the mass had to be preceded by some drainage of the colon.

A left inguinal colostomy was performed, and at the time of this operation it was possible to assure oneself of the absence of any metastases in the liver or of any involvement of the omentum or pelvic peritoneum. Advantage was taken of the general anaesthesia to determine the local operability of the huge growth and to decide to what extent the genital tract need be sacrificed.

The condition of rectum, vagina, and perineum rapidly improved as a result of the deflection of the faecal stream, and irrigation of the bowel and vagina soon rendered possible the extirpation envisaged. An abdomino-perineal excision of the rectum with removal of the uterus and vagina was performed, along with a small portion of the bladder: the patient made a good recovery.

All went well for six years, when a recurrence took place in the inguinal glands of the left groin. This was ulcerated and past removal by the time the patient made known her condition, and she died from haemorrhage from a large artery. There was no evidence of any abdominal or pelvic recurrence.

Carcinoma of rectum infiltrating the prostate and vesiculae seminales: abdomino-perineal excision with prostato-vesiculectomy.—A somewhat remarkable case is the following: A man aged 35 had a huge carcinoma of the rectum, infiltrating prostate and vesiculae seminales. The latter were removed along with the rectum, and the membranous urethra was attached to the neck of the bladder over a catheter. For some weeks urinary leakage ensued from the perineal wound. Providence sometimes kindly interferes on the surgeon's side: the perineal wound finally healed, but, alas, the patient was incontinent, and for 33 years has controlled urination by means of a soft rubber catheter tied round the root of his penis. A fair amount of the time since his operation has been spent in Her Majesty's gaols, but when I met him a year or two ago he assured me that he was "going straight." It is difficult to withhold admiration from a man with a colostomy and a "garrotted" root of the penis who can indulge in games of chance and hazard with the police force. Thirty-two years have passed since his operation.

Carcinoma of rectum: abdomino-perineal excision: survival of 33 years.—A spinster aged 35 had a large ulcerating carcinoma of the rectum, almost surrounding the ampullary portion of the rectum. Abdomino-perineal excision. Patient well 33 years later.

Canon H. was operated on for a carcinoma of the rectum in 1931: a perineo-abdominal excision was performed. He required a transurethral resection of his prostate before 1939, and underwent a successful partial gastrectomy for a bleeding ulcer during the last war. He died from old age a few weeks ago, but there had been no recurrence of his cancer in the 27 years that had elapsed.

Metastases in the Liver

The high fertility of hepatic tissue as a soil for tumour-cell proliferation has often been commented on. This fertility determines (*a*) a high incidence of "takes" for the initial neoplastic emboli entering the liver, and (*b*) an increased rate of proliferation of the cells of the established deposit.

Nevertheless, Lloyd-Davies's (1957) case of excision of the right lobe of the liver for a metastasis survived three and a half years.

The incomputable factor in cancer prognosis enabled almost 10% of palliative operations in Lockhart-Mummery's (1958, personal communication) recent collective series to survive five years, one even 10 years. The average survival was 1.7 years.

Carcinoma of the Kidney

In the case of renal carcinoma early metastases are more frequent in high-grade malignant growths. The histological grade of the tumour seems to be the most important single factor in the prognosis; nevertheless in Sir Eric Riches's series certain cases with anaplastic growths and without irradiation were known to have survived 15, 13, and 8 years after operation.

On the other hand, Riches (1958) in his series found metastases present at the time of nephrectomy in 9% of cases, and in only one, situated in the chest wall, was it possible to perform a separate excision: however, this patient was alive five years later.

Per contra, metastases may not appear until six, eight, or ten years later, as in cases reported by Clairmont, Albrecht, and Fischer, and by Broster (1923, 1930): in Broster's patient fracture of the femur from a secondary growth took place nine years after nephrectomy.

Still more remarkable was a case of my own where I had performed a nephrectomy for a hypernephroma 23 years before the man came under Reginald Murley's care with a secondary hypernephroma at the lateral end of his clavicle. Despite *x*-ray therapy and later surgery, the secondary tumour which had lain dormant so long now ran a relatively rapid course, and the man died within a year with multiple deposits in the lungs.

Wilms Tumour

The prognosis for a unilateral Wilms tumour is still doleful, although more recent reports, especially from the Children's Hospital, Boston, U.S.A., suggest more grounds for optimism. The prognosis for bilateral Wilms tumour is indeed devastating, although Ladd had a survival of 15 years in a patient treated by right nephrectomy with pre- and post-operative radiotherapy followed by intensive radiotherapy to the opposite kidney.

P. P. Rickham (1957), of Liverpool, reported a case of bilateral Wilms tumour treated by nephrectomy and

excision of the tumour on the opposite side followed by radiotherapy: the child was still alive five years later.

Sir Eric Riches's wonderful case, where he removed a Wilms tumour in a girl of 2½ years, has now, 24 years later, two children of her own. She had no *x*-ray therapy at the time of her surgery.

Osteoblastic Sarcoma and Sarcoma of Tendon-insertions

I have written so often about the "hindquarter" operation that I hesitate to make even the briefest reference to the procedure or to the patients for whom it is required. Some of the good results are doubtless due to the grading of the malignant tumour, but others seem to involve the patient's own resisting power to malignancy.

A woman seven months pregnant had an osteoblastic sarcoma of the upper end of the femur. The pregnancy was terminated and a hindquarter amputation performed. She is free from recurrence 14 years later.

A girl aged 18 had a huge tumour of the upper end of the left thigh: there was a pathological fracture of the femur at the level of the great trochanter. A hindquarter amputation was performed in the Sydney Hospital in June, 1947: the tumour was a sarcoma originating in the insertion of the gluteal muscles. The patient is alive and free from recurrence more than 11 years later.

Melanoma

The behaviour of no other tumour is so unpredictable as that of a melanoma: only rarely is a frankly malignant growth cured by excision, and it has been said of malignant melanoma that it is "virtually a death warrant." It is, however, germane to my thesis of cancer resistance that occasionally even a melanoma which has metastasized undergoes spontaneous retrogression.

James McClure (1936) records the case of a malignant melanoma in the vicinity of the eyebrow of a colleague, in whom there was already an infected lymph node in the neck. About a year after operation followed by radium treatment a recurrence appeared in the neck: this was excised and the patient survived operation without further recurrence and died 32 years after the initial surgical removal (*Brit. med. J.*, 1954).

Still more wonderful are Hogarth Pringle's (1937) two cases. In the man of 30 years there was a melanoma of the medial aspect of the left thigh, and the inguinal and lower external iliac lymphatic nodes were already invaded: he was operated on by the technique associated with Hogarth Pringle's name and remained free from recurrence 30 years later.

Even more remarkable was the girl of 17 with a melanoma of the flexure of the left elbow and with axillary gland involvement. She was alive 38 years later, having survived the anxieties of several pregnancies.

In comparison with these long survivals one of my own seems of little moment. The Seigneur of one of the districts in the Channel Islands had a melanoma of the skin of the cheek and a number of infected cervical nodes. The lesion of the cheek was widely excised and grafted: a block dissection of the neck was performed on the same side. Contrary to all expectations the man lived 20 years and died of an intercurrent malady.

A woman had a melanoma of the right buttock excised by the late Professor Grey Turner. Five years later some abdominal discomfort led to the diagnosis of appendicitis and a laparotomy revealed the presence of melanotic lymphatic nodes along the course of the external iliac vessels. The abdomen was closed and a hopeless prognosis was given. Further consultation suggested a hindquarter amputation, since it was felt that by this procedure there was a better chance of extirpating the lymph channels from the site of the original tumour in the buttock through the sciatic notch to the iliac glands. The patient has now passed six and a half years without recurrence of the melanoma.

An extraordinary case was reported by A. C. Allen (1949). A woman was first seen in 1942 with a melanoma of the right forearm, which was excised: a year later a melanomatous mass in the scar was removed. Nearly a year later, during the seventh month of a pregnancy, there was wide dissemination of secondaries. By the third month after parturition all the nodules had disappeared, except in the right groin. She was entirely well 12 years later.

Regression may take place unexpectedly in the most malignant of tumours as in the case reported by Sumner (1953). The patient was a woman of 30 who had a malignant melanoma with secondaries in the skin, breast, and inguinal lymph nodes. Some of the larger tumours were removed as a purely palliative procedure. Seven and a half years after the original tumour was first seen she was alive and well.

Intraocular Melanoma

In the case of intraocular melanomata a number of examples of long delay before metastases make their appearance have been recorded. The interval between enucleation of the eye and the appearance of metastases in the case recorded by Webb-Johnson and MacLeod (1924) was 18 years: Cairns (1922) saw orbital recurrence and a large metastasis in the scapula 18 years after enucleation of the eye: Mori (1913) encountered widespread metastases 15 years after the eye operation: Dawson (1922) and Elsberg (1928) each met with cases metastasizing at 14 years, and Wilbur and Hartman (1931) reported cases with intervals of 13, 10, and 10 years after removal of the eye. One of the longest intervals was in a case of Essex Wynter (personal knowledge) — 30 years — but the delayed interval metastasis of 32 years in Wilder's (1900) case is probably the longest recorded.

In one case of my own an unsuspected metastasis of absolutely minute size was removed from a breast, mainly to relieve the anxiety of the patient, who had been fearful of a primary mammary tumour. An eye had been removed six years before: the mammary tumour was discovered to be a melanotic metastasis by the histologist outside the operating theatre and proved to be the harbinger of abdominal metastases in the course of the next few months. I have also encountered a hepatic metastasis 12 years after eye-enucleation for melanoma.

Many more than 20 years must have elapsed before generalized dissemination closed the life of a Scottish gynaecologist who had lost an eye for an intraocular melanoma. The liver is the site *par excellence* for the recurrence in these patients with long-delayed metastases.

What fans the smouldering cinders to flame?

Conclusion

The incomputable factor in cancer prognosis! I make no boastful claim for surgical responsibility for those "successes" which I have ventured to place before you: many causal factors are concerned, not least the innate resisting power of the individual patient to cancer invasion. Sir James Barrie tells us somewhere that God gave us memory "that we might have roses in December." Those patients to whom I have referred are some of my "roses in December." I have wanted to share my roses with you. They are my sources of encouragement in the cancer fight: they are an earnest of the coming of "the rose-fingered dawn," when for the cure of cancer gross mechanical destruction and cruel mutilation of tissues shall perhaps no longer be required, nor the scorching methods and machinery of Hephaestus, the blacksmith god, or of Prometheus, who stole fire from heaven.

I will conclude with this message of confidence that was employed by Sir Alfred Pearce Gould in the closing sentence of his Bradshaw Lecture in 1910, and in the *ipsissima verba* of my old master: "We are apt to envy the astronomers who know so well the movements of the spheres, that they foretell the happenings of the universe with a precision that is the despair of workers in other branches of natural science. But with all their knowledge of these laws they cannot hasten on the day, or affect in one small circumstance the movement of a planet, or alter the destiny of a single grain of meteoric dust. But when the biologist shall know the laws that govern cell-growth, with a knowledge akin in its sweep and accuracy to that of the astronomer, he will have power, and that power will enable him to prevent, to control, and to cure cancer."

Research has taught us that that power is not so far distant from our grasp to-day.

REFERENCES

Allen, A. C. (1949). *Cancer*, **2**, 28.
Banks, W. Mitchell (1878). *Liverpool and Manchester Medical and Surgical Reports*, p. 192
—— (1893). *The Gentle Doctor*. Lee and Nightingale, Liverpool.
Bowlby, Sir Anthony (1925). *Brit. med. J.*, **1**, 234.
Brit. med. J., 1954, **2**, 1234.
Broster, L. R., (1923). *Brit. J. Surg.*, **11**, 287.
—— (1930). *Proc. roy. Soc. Med.*, **23**, 551.
Bryant, T. (1902). *Brit. med. J.*, **1**, 1200.
Cade, Sir Stanford, and Lee, E. S. (1957). *Brit. J. Surg.*, **44**, 433.
Cairns, F. D. (1922). Ibid., **10**, 290.
Clifton, J. A., Philipp, R. J., Ludovic, E., and Fowler, W. M. (1952). *Amer. J. med. Sci.*, **224**, 121.
Cole, W. H., Roberts, S., Watne, A., McDonald, G., and McGrew, E. (1958). *Bull. N.Y. Acad. Med.*, **34**, 163.
Dawson, H. G. W. (1922). *Brit. med. J.*, **2**, 757.
Elsberg, C. A. (1928). *Surg. Gynec. Obstet.*, **46**, 1.
Engell, H. C. (1955). *Acta chir. scand.*, Suppl. 201.
Franks, L. M. (1954). *Ann. roy. Coll. Surg. Engl.*, **15**, 236.
—— (1956a). *Lancet*, **2**, 1037.
—— (1956b). *J. Path. Bact.*, **72**, 603
Gillies, Sir Harold (1949). *Proc. roy. Soc. Med.*, **42**, 176.
Gordon-Taylor, Sir Gordon (1938). *Brit. med. J.*, **2**, 1071.
—— (1948). *Ann. roy. Coll. Surg. Engl.*, **2**, 60.
Gould, A. P. (1882). *Trans. med. Soc. Lond.*, **6**, 177; *Lancet*, **1**, 560.
—— (1892). *Lancet*, **1**, 411.
—— (1910). Ibid., **2**, 1665.
Hadfield, G. (1954). *Brit. med. J.*, **2**, 607.
Heath, C. (1871). *Lancet*, **1**, 847.
—— (1898). *Brit. med. J.*, **2**, 1783.
His, W. (1870). *Arch. mikr. Anat.*, **6**, 229.
Kettle, E. H. (1912). *J. Path. Bact.*, **17**, 40.
Lloyd-Davies, O. V. (1957). *Brit. J. Surg.*, **45**, 113.
McClure, J. (1936). *Lancet*, **2**, 371.
Manson, J. S. (1922). *Brit. med. J.*, **1**, 996.
—— (1925). Ibid., **1**, 234.
Moore, C. H. (1867). *Med.-Chir. Trans.*, **50**, 245.
Mori, T. (1913). *Frankfurt. Z. Path.*, **12**, 2.
Newcomb, W. D. (1936). *Proc. roy. Soc. Med.*, **30**, 113.
Nicholson, G. W. (1923). *Guy's Hosp. Rep.*, **73**, 164.
Papanicolaou, G. N. (1954). *Atlas of Exfoliative Cytology*. Harvard Univ. Press, Cambridge, Mass.
Pringle, J. H. (1937). *Lancet*, **1**, 508.
Raeburn, C., and Spencer, H. (1953). *Thorax*, **8**, 1.
Riches, E. W. (1958). *Trans. med. Soc. Lond.*, **74**, 132.
Rickham, P. P. (1957). *Brit. J. Surg.*, **44**, 492.
Roberts, S., Watne, A., McGrath, R., McGrew, E., and Cole, W. H (1958). *A.M.A. Arch. Surg.*, **76**, 334.
Steward, F. J. (1925). *Brit. med. J.*, **1**, 156.
Sumner, W. C. (1953). *Cancer*, **6**, 1040.
Trinkle, A. J. (1936) *Amer. J. Cancer*, **27**, 676.
Verneuil (1888). *Sem. méd. (Paris)*, **8**, 112.
Webb-Johnson, A., and Macleod, C. E. A. (1924). *Brit. med. J.*, **1**, 314.
Wilbur, D. L., and Hartman, H. R. (1931). *Ann. intern. Med.*, **5**, 201.
Wilder, W. H. (1900). *J. Amer. med. Ass.*, **35**, 1363.
Willis, R. A. (1953). *Pathology of Tumours*, 2nd ed. Butterworth, London.

TREATMENT OF HYPERTENSION WITH PENTOLINIUM AND MECAMYLAMINE

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Ganglion-blocking agents are now recognized as being the treatment of choice for the more severe forms of hypertension. The ideal ganglion-blocking agent has yet to be found, and in the meantime there is a temptation to turn too readily to each new preparation as it appears, without properly evaluating its predecessors.

At the present time, therefore, when new ganglion-blocking agents are continually being put at our disposal, two of which are currently being used in this department, it seemed worth while to consider what measure of long-term control could be obtained by means of pentolinium and mecamylamine, both of which have now been widely used. The present paper is based on our experience of these drugs in the treatment of 78 patients with severe hypertension between April, 1954, and May, 1958.

Selection of Patients

Of the 78 patients in the present series, 47 were judged to have malignant hypertension from the level of the diastolic blood pressure and the presence of papilloedema. The remaining 31 all had severe benign hypertension with diastolic pressures over 120 mm. Hg and lesser grades of retinopathy. Several of these patients were probably in a pre-malignant phase in view of the progressive retinopathy. We wish to emphasize that we have not included patients with mild benign hypertension and a diastolic pressure below 120 mm. Hg in this series. All patients with these criteria were treated with ganglion-blocking agents unless some contraindication to treatment was present. A raised blood urea, recent cardiac or cerebral thrombosis, and severe cerebral arteriosclerosis were all considered to be partial but not absolute contra-indications. Each patient was judged on his or her

merits, and even those with limited life expectancy were treated if sight was deteriorating. The age range of patients varied from 15 to 65 years, average 44.7 years; 46 were males, and 32 females. The aetiology of the hypertension was varied; a number with pre-existing renal disease are included.

Use of Reserpine

It is well recognized that reserpine, in addition to exerting a mild hypotensive effect in 41% of patients when used alone (Platt and Sears, 1956), is similarly useful in conjunction with a ganglion-blocking agent. In this way it is often possible to achieve a satisfactory blood-pressure level with a lower dose of the blocking agent and hence fewer side-effects. It has therefore been our standard practice to use both types of treatment whenever possible. In order to avoid subsequent interference with stabilization from the delayed effect of reserpine, we consider that, when possible, treatment with the latter should be started immediately the patient is seen in the out-patient clinic. In this way it will be apparent by the time of admission either that reserpine is having no effect, in which case it is discontinued, or that it is already exerting its usual hypotensive effect, to which the ganglion-blocking agent is added. In exceptional patients, not included in this study, reserpine alone was adequate to control even severe hypertension. In patients with malignant hypertension in whom the sight is threatened, it is unjustifiable to delay treatment with pentolinium or mecamylamine, and in these circumstances reserpine was started simultaneously with the ganglion-blocking agent.

In-patient Stabilization

All patients in this series were admitted to hospital for initial stabilization. On the assumption that the urgency of the symptoms did not necessitate immediate treatment the patient was allowed a few days on reserpine alone, in order to provide a baseline for the blood-pressure readings. During this period no attempt was made to enforce bed rest, unless it was necessary on other counts. After a satisfactory baseline had been obtained, the ganglion-blocking agent was started. In the case of pentolinium, the usual starting dose for uncomplicated patients was 20 mg. four times a day, 20 to 30 minutes before the main meals—that is, at 7.30 a.m., 12.30 p.m., 5.30 p.m., and 10.30 p.m. We consider that this constant time relation to meals is important in ensuring a consistent rate of absorption. If accumulation of the drug due to renal impairment seemed likely, twice daily dosage, at 7.30 a.m. and 5.30 p.m., was used. Mecamylamine was usually given orally twice daily, at 7.30 a.m. and 5.30 p.m., in the first instance, starting at 5 mg. a dose.

Thereafter, in either case, the blood pressure was taken lying and standing, each day at the same time, which as a matter of convenience was arbitrarily fixed at 10.30 a.m. The dose was steadily increased at daily intervals, or less often as determined by the blood-pressure response and the possibility of retention owing to impaired renal function, until a hypotensive effect was obtained. The blood pressure was then recorded hourly on one or more days. In this way the duration of action of a single dose was assessed, and the frequency of administration necessary to achieve a continuous hypotensive response determined. This response was reassessed as often as necessary until a satisfactory result was obtained.

It was found that in most cases three or four doses of pentolinium were required daily, but only two or three of mecamylamine. Some patients with renal impairment might be controlled on one dose a day, or even every other day. The total daily dose was usually evenly divided between the individual doses, but it was sometimes necessary to give more at one time of day than at another.

Out-patient Supervision

All patients were seen, at intervals of one to four weeks after discharge from hospital, by one of us (H. T. N. S.) in a clinic exclusively concerned with the management of hypertensive patients. Whenever possible an attempt was made to see the patient at the same time of day on each visit. At these interviews the blood pressure was taken three times, both lying and standing, and the lowest reading in each posture was recorded. The dose was adjusted according to the blood-pressure response and the ocurrence of any side-effects. The patient was thereafter seen at intervals as necessary.

One of the most important points emerging from the out-patient supervision of our hypertensive patients was the necessity for frequent, often minor, alterations in the regime in order to control side-effects, while maintaining effective levels of dosage. Intelligent co-operation on the part of the patients was found to facilitate control of treatment, and, by contrast, in an unintelligent patient control was more difficult and less satisfactory. Adequate time for interviews was important and in a three-hour session it proved impracticable to see more than 12 patients.

Dosage and Tolerance

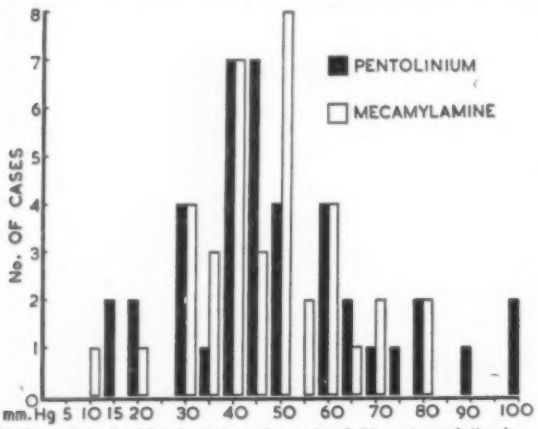
There was considerable individual variation in tolerance to these drugs, as reflected in the range of dosage employed, which with pentolinium ranged between 20 and 640 mg. a day, and with mecamylamine between 2.5 mg. every third day, and 80 mg. daily. In the case of pentolinium alteration in the completeness of absorption from patient to patient, and from time to time in the same patient, undoubtedly accounted for some of the changes; but since a similar, though less marked, phenomenon was noticed with mecamylamine, which is more or less completely absorbed, some variation of tolerance must be postulated. This usually necessitated a gradual increase of dosage, but occasionally the reverse was true.

Results

Of the 78 patients treated, 40 were given pentolinium and 25 mecamylamine; the other 13 were given both forms of treatment at different times. In regard to these 13 we have included (see Chart) only that fall in diastolic pressure recorded during treatment with the more effective of the two drugs. The initial diastolic pressure was taken as the mean of several in-patient readings—these usually being distinctly lower than those obtained in the out-patient department—and ranged between 120 and 220 mm., with a mean of 145 mm. Hg (median 145 mm.). No attempt has been made to indicate the accompanying fall in systolic pressure, which was more variable and often seemed unrelated to the severity of the disease.

Survival Rate

Since it is impossible to arrive at any accurate estimate of life expectancy in untreated benign hypertension, the effect of ganglion-blocking agents on survival has been considered only in relation to the 47 patients with malignant hypertension, in which condition a fairly clear-cut prognosis exists in the untreated state. Both pentolinium and mecamylamine had similar effects on the diastolic pressure, and it seemed unlikely that there could be any significant difference between the two on the survival rate. For this reason, and since the number of patients available was small, no attempt has been made to compare the effect of the two preparations in this respect.



Fall in diastolic blood pressure in each of 78 patients following treatment with either mecamylamine or pentolinium.

Of the 47 patients, 13 died, 8 (62%) within the first six months of treatment. Most of them were patients with already advanced disease in whom treatment was instituted too late to prevent irreversible damage.

After the first six months, the death rate was much lower and the Table shows the survival rates for our patients compared with those for untreated patients reported by Keith *et al.* (1939) and Kincaid-Smith *et al.* (1958). The number of patients observed is too small to justify statistical analysis of the survival rate, and some anomalies are apparent, such as the 95% survival in the small group observed for 24 months.

Retinopathy

With two exceptions (one patient in whom the blood pressure was never effectively controlled and another who had a blood urea of 188 mg. per 100 ml. at the start of treatment and died four months later) all patients with severe hypertensive retinopathy showed marked improvement. In all patients with papilloedema this resolved in from two to four months, there being in these and other patients a corresponding decrease or disappearance of exudates and haemorrhages. In most patients, including those originally with papilloedema, the only residual abnormalities were variation in the calibre of the retinal arteries and "nipping" of the veins at the arterial crossings.

Comparison of Survival Rates

Period of Observation up to Closure of Series	*No. at Risk	No. Surviving at Stated Interval after Starting Treatment	Survival Rate		
			Present Series	Keith *et al.* (1939)	Kincaid-Smith *et al.* (1598)
6 months	42	36	86%	46%	20%
12 "	37	30	81%	21%	10%
18 "	26	23	88%	13%	6%
24 "	21	20	95%	12%	5%
30 "	12	10	83%	8%	4%

*The "number at risk" for each period of observation includes all patients who either have been observed for that period or could have been had they lived; it excludes patients entering the series too recently for this period of observation to have been completed. For instance, a patient entering the series—that is, beginning treatment—15 months before it was closed, whether now alive or dead, is considered as "at risk" in the follow-up at 6 and 12 months but not for the longer periods of observation.

Side-effects and Complications

One of the most important limiting factors in the use of ganglion-blocking agents is the presence of side-effects, most of which are due to the unwanted suppression of parasympathetic activity. The most common complaints in order of frequency were constipation, dryness of the mouth, paralysis of accommodation, hesitancy of micturition, and occasionally impotence.

On the whole, side-effects were more noticeable with mecamylamine than with pentolinium. Constipation was disproportionately severe with mecamylamine, and in one patient led to paralytic ileus with intestinal obstruction. Paralytic ileus due to mecamylamine, presenting as a surgical emergency, has also been reported by Grant and Boyd (1957).

In this connexion it is interesting to note that Bennet *et al.* (1957) emphasized that mecamylamine has other actions than those of a ganglion-blocking agent, including a direct post-ganglionic depressant effect on the contraction of intestinal muscle. They suggest that this is the reason for the unduly high incidence of intestinal side-effects with mecamylamine.

Another hazard of constipation was the sudden development of profound hypotension, presumably due to the more complete absorption of the drug consequent upon the intestinal stasis. The fact that this complication occurred in our experience only with pentolinium is in conformity with the view that mecamylamine is completely absorbed under normal conditions.

Because of the dangers, as well as the discomforts of constipation, brought about by these agents, we pay particular attention to measures designed to counteract it. These include "All Bran" for breakfast, and when necessary a standardized senna preparation at night; but if, despite such steps, constipation continued, we often thought it wiser to reduce the dose of ganglion-blocking agents temporarily than to run the risk of the complications mentioned.

In addition to the side-effects common to all ganglion-blocking agents, mecamylamine was found to possess two other effects, apparently peculiar to itself. One was the development of a coarse tremor, which we observed in two patients. In the first of these, its significance not being immediately realized, mecamylamine administration was continued for a short time and led to the development of a psychotic state. The patient, a 35-year-old man, was suffering from chronic renal disease and hypertension. Despite a blood urea of 156 mg. per 100 ml., it was decided to start treatment with mecamylamine in view of the severe retinopathy. The dose was gradually increased to 45 mg. daily, by which time he noticed a coarse tremor of the hands, which became worse over the next

few days. On the fourth day he became confused and hallucinated, the clinical picture being that of delirium tremens. Mecamylamine was stopped, but the tremor and psychosis persisted for 10 days before recovering.

A second patient, a 49-year-old man, developed a coarse tremor and mental confusion while receiving 80 mg. of mecamylamine daily. In this patient the blood urea was 78 mg. per 100 ml., and here again the symptoms cleared up on stopping mecamylamine.

Similar effects have been noted by others (Doyle and Neilson, 1956; Schneckloth *et al.*, 1956; Deming *et al.*, 1957; Harington and Kincaid-Smith, 1958), and a suggestion has been made that the tremor is due to the associated uraemia (Greenberg and Davidson, 1958).

We do not think that the tremor in our patients resembled the twitching which occurs in some uraemic patients, usually with very high levels of blood urea, and we are convinced that both the tremor and the psychosis were due to the mecamylamine. In support of this contention Schneckloth *et al.* (1956) noted that of their seven patients showing these effects only four were notably uraemic. The other three had blood ureas of 27 mg., 45 mg., and 50 mg. per 100 ml. respectively.

A second side-effect of mecamylamine, the complaint of feeling "drugged" while receiving therapeutic doses, is perhaps even more important because of its ubiquity. Smirk and McQueen (1957) also noted this side-effect with mecamylamine, although not with pentolinium, but did not emphasize its importance. In our experience, this lack of well-being was the commonest complaint of patients taking mecamylamine and materially added to their discomfort. It was one of our main reasons for changing to an alternative preparation.

Discussion

There is no doubt that both pentolinium and mecamylamine are potent hypotensive agents. We are not, however, here concerned merely with their effect on the blood pressure, but with the no less important effects on the patient as a whole and their suitability for long-term use. In this respect so much depends on the patient's subjective impressions that blood-pressure figures alone are totally inadequate, and we have therefore been forced to rely in part on clinical impressions.

It should be made clear that whilst we have tried to achieve a satisfactory drop in blood pressure we have not, except in a few patients, aimed at normal levels. The conversion of a symptom-free patient with a dangerously high blood pressure to one with reasonably normal levels but severe side-effects is a common experience, and one which we tried to avoid by aiming at a more modest reduction in blood pressure to relieve any symptoms originally present, without substituting others caused by the treatment. Our results must therefore be considered in the light of these views, for the figures do not represent the lowest levels which could be obtained, but rather the optimum lowering commensurate with well-being. With relatively short-acting preparations such as mecamylamine and pentolinium it is difficult to obtain a satisfactory continuous lowering of the blood pressure, but even with the relatively imperfect control at present obtainable without imposing too many restrictions on the patient it is gratifying and perhaps surprising that the severe retinopathy, including papilloedema, is so much improved as a result of treatment.

The most important yardstick by which to assess improvement is survival. Between 79% (Keith *et al.*, 1939) and 90% (Kincaid-Smith *et al.*, 1958) of untreated cases of malignant hypertension end fatally within a year; by comparison 81% of our cases were alive one year after treatment started. Smirk (1954) reported that 75% of patients with malignant hypertension were alive after 18 months' treatment with hexamethonium, and our figure is very similar. Six of our patients are still under treatment after at least four years.

On the debit side both pentolinium and mecamylamine require careful stabilization and continual time-consuming supervision in order to obtain and maintain a satisfactory depression of blood pressure, which even at best still fluctuates fairly widely. In addition to these difficulties of control were the side-effects already mentioned, which were most marked with mecamylamine. All those patients who had experience of both pentolinium and mecamylamine preferred the former, and we have now stopped using mecamylamine.

We conclude, therefore, that in our experience both pentolinium and mecamylamine are powerful hypotensive agents capable of saving sight and prolonging life. Both have their imperfections; but, of the two, pentolinium is to be preferred as having fewer and less severe side-effects, enabling the patient to live a relatively normal life. Whether one of the newer ganglion-blocking agents will eventually supplant pentolinium only further experience will show.

Summary

We describe our experiences in the control of 78 severely hypertensive patients with pentolinium and mecamylamine extending over four years. Side-effects, which occur with both preparations, were more numerous and severe in the case of mecamylamine; in our opinion this outweighed the advantage of its more constant absorption and rendered it unsuitable for long-term use. In some patients the synergistic effect of reserpine enabled the dose of ganglion-blocking agents to be reduced, with a concomitant decrease in the severity of side-effects. Despite the shortcomings of both preparations the results achieved have been most gratifying as regards both the prolongation of life and the restoration and preservation of sight. New ganglion-blocking agents are now available which, from a short acquaintance, seem to offer certain advantages over the older preparations, but it remains to be seen whether they will stand the test of long-term use or be able to improve significantly upon the results already obtained.

We thank Professor R. Platt and Professor D. A. K. Black for their invaluable advice on the preparation of this paper, and for allowing us to study patients under their care.

References

Bennet, G., Tyler, C., and Zaimis, E. (1957). *Lancet*, **2**, 218.
Deming, Q. B., Hodes, M. E., Edreira, J. G., and Baltazar, A. (1957). *New Engl. med. J.*, **256**, 739.
Doyle, A. E., and Neilson, G. H. (1956). *Brit. med. J.*, **2**, 1431.
Grant, A. P., and Boyd, J. S. (1957). *Lancet*, **1**, 713.
Greenberg, M., and Davidson, E. (1958). Ibid., **1**, 641.
Harington, M., and Kincaid-Smith, P. (1958). Ibid., **1**, 499.
Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, **197**, 332.
Kincaid-Smith, P., McMichael, J., and Murphy, E. A. (1958). *Quart. J. Med.*, **27**, 117.
Platt, R., and Sears, H. T. N. (1956). *Lancet*, **1**, 401.
Schneckloth, R. E., Corcoran, A. C., Dustan, H. P., and Page, I. H. (1956). *J. Amer. med. Ass.*, **162**, 868.
Smirk, F. H. (1954). *Brit. med. J.*, **1**, 717.
—— and McQueen, E. G. (1957). Ibid., **1**, 422.

SJÖGREN'S SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS

BY

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For some time there has been evidence that Sjögren's syndrome is a "collagen disease" (Cardell and Gurling, 1954; Ramage and Kinnear, 1956). As the capacity of connective tissue to react to injury is limited to a few basic patterns, probably few "collagen diseases" are worth considering as separate entities. Any evidence demonstrating that what are now thought to be two separate "collagen diseases" are really different forms of the same disease is therefore desirable. In this paper clinical and pathological evidence is produced showing that Sjögren's syndrome may be a chronic and relatively benign form of systemic lupus erythematosus.

Systemic L.E. is a disease of connective tissue characterized by a prolonged intermittent clinical course during which a variety of organ systems may be involved in an episodic manner. Pathologically it is characterized by the presence of the L.E. factor, which is a protein or protein-bound substance present in all the body fluids and exudates and is responsible for the L.E. cell phenomenon and the formation of haematoxyphil bodies.

The most striking feature of Sjögren's syndrome is a diminution or cessation of secretions from the lacrimal and salivary glands and from the submucous glands of the respiratory and upper alimentary tracts; it is often associated with other systemic disturbances, the most common of which is rheumatoid arthritis.

Its pathological features have been well described by Sjögren (1943).

Lacrimal and Salivary Glands.—In the lacrimal glands connective-tissue proliferation and fibrosis are pronounced. Hyaline nodes may form in the glandular parenchyma and there is marked atrophy of the glandular tissue. Considerable round-cell infiltration occurs, chiefly by lymphocytes and plasma cells. The walls of the blood vessels are often thickened by hyaline tissue. Similar changes occur in the salivary glands, including the small glands of the mouth, nose, pharynx, and larynx. In the parotid and probably the other salivary glands lymphoid follicles may develop; these have not been seen in the lacrimal glands.

Conjunctiva.—The bulbar conjunctiva is oedematous in both the epithelial and the subepithelial layers. The epithelial cells become swollen and their nuclei are often enlarged and possess more or less conglomerated chromatin. Marked thinning of the epithelium occurs in the later stages of the disease. In the subepithelial tissue there is early destruction of elastic tissue, and hyalinization of the connective tissue is sometimes very pronounced. Close beneath the epithelium there is infiltration with round cells, mostly plasma cells. The goblet cells, mainly found in the fornices, are very swollen and are present in increased proportions.

Cornea.—The epithelial changes are similar to those of the conjunctiva. In addition, however, in the substantia propria of the cornea and in the sclera small sharply defined areas may be seen. These are generally oval in shape and in unstained preparations show a slight brownish tint. With haematoxylin they stain blue. The exact nature of the change which causes them is not known.

Clinical and Pathological Investigations

I saw 28 consecutive cases of Sjögren's syndrome at the Bristol Eye Hospital in a period of nine months. In each case a history was taken and a physical examination carried out. Urinary albumin, haemoglobin, full blood count, E.S.R., and electrophoresis of the serum proteins were done and the peripheral blood was examined for L.E. cells, using the coagulated blood technique on three occasions at intervals of about three weeks. Tables I and II summarize the salient points of this investigation.

TABLE I.—*Salient Features of 28 Cases of Sjögren's Syndrome*

	No. of Cases
Rheumatoid arthritis	17
Arthralgia	9
Chilblains and/or Raynaud's phenomenon	12
Purpura	7
Photosensitivity	4
Thyroid disease	4
Colitis	2
Hypochromic anaemia	5 out of 27
Leucopenia	5 out of 27
Thrombocytopenia	16 out of 26
Raised E.S.R.	14 out of 26
Lowered albumin	15
Increased α_2- globulin	16
" γ- "	17
L.E. cells present	10

Pathological Similarities Between Sjögren's Syndrome and Systemic Lupus Erythematosus

Most students of Sjögren's syndrome have assumed that the corneal and conjunctival changes are due only to the reduced secretion of tears; hence the name keratitis sicca. There is, however, a good deal of evidence against this view. Firstly, as Sjögren has pointed out, the eye does not look dry, and with the slit-lamp the globe is seen to be covered with a fluid layer. Secondly, staining of the cornea and conjunctiva in the characteristic fashion with rose Bengal is not well correlated with lack of tears as shown by Schirmer's test; many elderly people have a deficiency of tears yet have no other signs or symptoms of Sjögren's syndrome; on the other hand, some patients who present symptoms of the disease and whose eyes stain in a typical manner with rose Bengal possess almost a normal tear supply (Henderson, 1950). Thirdly, the pathology of Sjögren's syndrome is very different from that which occurs in conditions such as lagophthalmos, in which there is dryness of the eyes. In these conditions keratinization is the characteristic pathological process as in any other mucous surface subject to drying. Keratinization occurs only in very severe Sjögren's syndrome, and then to a slight degree; in these cases the bulb does tend to lose its natural sheen.

It is unjustifiable, therefore, to regard the ocular changes as being brought about solely by desiccation of the epithelium. This was pointed out by Sjögren. He thought the changes in the eye could be explained as compensatory attempts by the conjunctiva to secrete fluid to make up for the lack of tears. The changes in the goblet cells in the lower fornix could be explained in this way, but not the other changes in the cornea and conjunctiva.

A review of the histology of Sjögren's syndrome shows how well it accords with that of systemic lupus. Oedema, early destruction of elastic tissue, hyalinization, infiltration with lymphocytes and plasma cells, fibroblastic proliferation, and thickening of blood-vessel walls with hyaline tissue all occur in systemic L.E. The

TABLE II.—*Clinical and Pathological Features of 28 Patients with Sjögren's Syndrome*

Case No.	Age and Sex	Duration of Ocular Symptoms in Years	Joints	Skin	Hb (g.%)	E.S.R. Wintrobe mm./1 hr.	W.B.C. (c.mm.)	Platelets (c.mm.)	Serum Protein (g.%)	Albumin (%)	α_2 Globulin (%)	γ Globulin (%)	L.E. Cells	Remarks
1	57 F	2	Arthralgia	Purpura. Koilonychia	15·5	15	5,000	180,000	6·5	44	13	21	None	(L) Horner's syndrome. No cause found
2	66 F	3	,,	Chilblains	15·9	11	7,300	205,000	7·6	49	8	24	,,	
3	43 F	5	Rheum. arthritis	Erythematous rash on face	11·7	19	8,000	113,000	7·6	53	10	19	,,	Iron-deficiency anaemia. Thyroidectomy, 1953. No histological report
4	59 F	3	,,	Chilblains	11·5	44	5,700	320,000	7·3	45	13	23	Numerous	Coombs test negative. Perforated corneal ulcer. Cytoid body in retina
5	53 F	10	Arthralgia	Rosacea facies	13·5	9	6,700	350,000	7·0	54	12	17	None	
6	51 F	4	,,	Chilblains. Psoriasis	13·5	20	8,000	290,000	6·8	60	10	13	,,	
7	66 F	6	Rheum. arthritis	Normal	13·3	49	1,200	173,000	7·7	48	8	27	,,	Recurrent bilateral uveitis 4 years. No cause found. *X*-ray chest: hilar adenopathy, fine nodularity through all zones of both lungs — appearance compatible with lupus lung.
8	59 F	2	,,	Raynaud's phenomenon. Psoriasis	15·5	15	4,400	340,000	7·5	60	5	15	,,	Bilateral uveitis 4 yrs. No cause other than toxoplasmosis. Dye test 1/32; complement-fixation test positive 1/4
9	63 F	2	,,	Chilblains	14·1	15	3,600	210,000	7·0	59	10	12	,,	Recurrent iritis. No cause found
10	68 F	18	Normal	Purpura	17·8	3	8,400	195,000	7·8	57	8	16	,,	Is on delta-steroid and corticotrophin for arthritis
11	53 F	3	Rheum. arthritis	Photosensitivity	13·0	48	7,300	420,000	7·2	56	9	17	,,	
12	72 F	8	,,	Normal	13·5	17	5,000	200,000	7·0	Normal	Normal	Normal	,,	
13	74 F	11	Arthralgia	Raynaud's phenomenon. Purpura	13·6	37	5,700	169,000	7·2	48	10	14	Very few	β-globulin raised to 23%. Recurrent parotid enlargement for 10 years
14	75 F	4	Rheum. arthritis	Normal	13·6	40	2,300	110,000	7·8	51	6	28	None	Enlarged liver and spleen. Liver-function tests normal apart from proteins. Felty's syndrome. Goitre removed 1945. No histological report
15	54 F	3	,,	Purpura. Photosensitivity	16·5	5	8,000	200,000	5·4	54	10	14	,,	β-globulin raised to 18%
16	69 F	6	,,	Normal	14·4	40	5,700	320,000	7·6	40	14	23	1 found	,, ,,
17	48 F	5	,,	Dermatitis following gold injections	12·6	41	4,100	340,000	6·8	43	10	29	None	
18	47 F	7	,,	Raynaud's phenomenon. Photosensitivity	10·8	35	3,400	220,000	7·8	36	11	34	Moderate numbers	Iron-deficiency anaemia. Mitral stenosis—no history of rheumatic fever
19	60 F	13	Arthralgia	Raynaud's phenomenon	14·4	30	5,000	250,000	7·2	43	9	29	Small numbers	Coombs test negative. Petit mal since childhood and Jacksonian epilepsy 5 years. Arteriogram and air encephalogram normal. Recurrent colitis. Parotid swellings 3 years
20	35 F	7	Rheum. arthritis	Chilblains. Raynaud's phenomenon. Urticaria. Photosensitivity	13·9	22	8,000	230,000	8·3	32	13	34	Large numbers	Coombs test negative. Bronchospasm and attack of collapse (R) lower zone, final *X*-ray chest N.A.D. Episcleritis; perforated corneal ulcer
21	53 F	2	,,	Normal	Not done	Not done	Not done	Not done	8·6	46	13	23	Small numbers	(R) homonymous hemianopia 2 yrs. No cause found. B.P. 130/90. Recurrent colitis
22	60 F	3	Normal	Chilblains. Purpura	14·7	19	7,300	170,000	8·2	31	14	39	None	
23	60 F	3	Rheum. arthritis	Purpura	15·2	22	8,900	240,000	7·4	42	13	24	Small numbers	β-globulin raised to 16%. Severe mental depression. Goitre removed 1927 — no histological report
24	67 F	1	,,	Normal	11·4	Not done	2,700	Not done	6·8	43	6	36	Small numbers	Enlarged spleen. Bone marrow hypocellular. Felty's syndrome. Hypopyon ulcer, 1957
25	50 F	10	Arthralgia	Purpura. Chilblains	14·5	4	4,000	200,000	7·6	53	9	18	None	β-globulin raised to 15%. Diffuse enlargement of thyroid, no toxic signs
26	70 F	3	,,	Raynaud's phenomenon. Chilblains	14·8	26	4,700	190,000	7·6	54	7	24	,,	Albuminuria
27	62 F	10	Rheum. arthritis	Leg ulcers. No varicose veins	12·6	36	4,700	410,000	7·7	48	7	25	,,	
28	83 F	13	Arthralgia	Normal	9·8	31	4,100	380,000	7·4	52	10	23	Numerous	Iron-deficiency anaemia. Recurrent pleurisy

oval bodies found by Sjögren in the substantia propria of the cornea and in the sclera which stain blue with haematoxylin may well be haematoxyphil bodies. These were described by Klemperer *et al.* (1950) as being pathognomonic of systemic lupus and as originating in an alteration of the nuclei of mesenchymal cells. They are about the size of a lymphocyte or larger, stain purple blue with haematoxylin, and are chiefly ovoid or spindle-shaped. Cytochemical methods have shown that the bodies contain partially depolymerized desoxyribose-nucleic acid. Unfortunately an opportunity has not yet arisen in which these methods could be applied to the bodies that occur in Sjögren's syndrome.

The bulbar changes of Sjögren's syndrome occur in that part of the bulb which is most exposed to light and the slight mechanical trauma of blinking. Sensitivity to light is a prominent feature of systemic lupus; and the skin lesions tend to develop in areas subject to friction or mechanical trauma. It may be that sunlight and/or mechanical trauma are precipitating factors in the development of the corneal and conjunctival changes of Sjögren's syndrome.

Necropsies on nine patients with Sjögren's syndrome have been fully reported in the literature (Bruce, 1941; Reader *et al.*, 1951; Ellman *et al.*, 1951; Haas, 1951; Morgan and Raven, 1952; Morgan, 1954; Cardell and Gurling, 1954). In only one (Morgan, 1954) was systemic L.E. diagnosed. However, the diagnosis of systemic L.E. at necropsy is notoriously difficult. Many of the findings in these necropsies are very suggestive of systemic lupus. For example, pericarditis was found in four, pleurisy in three, interstitial pneumonitis in two, enlarged lymph nodes in five, splenomegaly and perisplenitis in two, hepatomegaly and changes similar to those of lupoid hepatitis in two, and arteritis in three. Most of these patients died rather mysterious deaths, and this is typical of patients dying with systemic L.E.

Clinical and Clinico-pathological Similarities Between Sjögren's Syndrome and Systemic L.E.

Tables III and IV list the clinical and clinico-pathological features common to Sjögren's syndrome and systemic L.E. The frequency of the various manifestations of systemic lupus and even more those of Sjögren's syndrome varies considerably from author to author. Some quite common features of systemic lupus (such as pericarditis and a false-positive W.R.) have rarely been looked for in Sjögren's syndrome, thus precluding an accurate estimate of their frequency.

It is of interest to note that Shearn and Pirofsky (1952) found photophobia in 18% of their cases of systemic lupus and "optic abnormalities" other than funduscopic ones in 47%. It is possible that some of these patients had Sjögren's syndrome.

L.E. Cells and Sjögren's Syndrome.—L.E. cells have rarely been found in Sjögren's syndrome (Morgan, 1954; MacLean and Robinson, 1954; McLenachan, 1956), but they have not been looked for before in a series of cases. Probably more would be found if these patients were examined for the presence of L.E. cells at intervals over several years, as it is well known that repeated examinations may be necessary to obtain a positive test. Not all known cases of systemic lupus have a positive L.E. cell test; Wilkinson and Sacker (1957), in reviewing several reported series of systemic lupus, found the average incidence of a positive L.E. cell phenomenon to be 82%. In many large surveys no false-positive tests have been found: but a positive L.E. cell phenomenon has been reported in severe drug reactions, especially to hydrallazine, and in a few cases of cirrhosis of the liver (Wilkinson and Sacker, 1957). In gross leucopenia the L.E. cell phenomenon may be negative owing to the low neutrophil polymorph count, as the test partly depends on the number of these cells present; it may also be negative in patients on steroid therapy (Dubois, 1956) (see Case 11).

Mikulicz's Disease.—Morgan and Castleman (1953) and Morgan (1954) have shown that Mikulicz's disease and Sjögren's syndrome are probably identical in that the pathological changes in the salivary glands in the two conditions are the same and clinically the two diseases are similar. In our series Cases 13 and 19

TABLE III.—*Clinical Features Common to Sjögren's Syndrome and Systemic Lupus*

	Sjögren's Syndrome	Systemic Lupus
Sex	85–95% female	80–90% female
Maximum incidence	40–60 years	30–50 years
Clinical course	Episodic	Episodic
Rheum. arthritis	Very common	Very common
Arthralgia	Common	Common
Raynaud's phenomenon and chilblains	,,	,,
Photosensitivity	Fairly common	Fairly common
Purpura	,, ,,	,, ,,
Alopecia	,, ,, (Weber, 1945; Thompson and Eadie, 1956; McLenachan, 1956)	,, ,,
Chronic leg ulceration	Rare	,, ,,
Enlarged parotids	Fairly common	Rare (Shearn and Pirofsky, 1952; Harvey *et al.*, 1954; Morgan, 1954)
Enlarged lymph nodes	,, ,, (Beetham, 1935; Reader *et al.*, 1951; Gurling, 1953)	Common
Splenomegaly	Fairly common (Beetham, 1935; Bruce, 1941; Holm, 1949; Cadman and Robertson, 1952; Gurling, 1953; Thompson and Eadie, 1956)	Fairly common
Hepatomegaly	Fairly common (Bruce, 1941; Cadman and Robertson, 1952, Gurling, 1953; McLenachan, 1956; Thompson and Eadie, 1956)	,, ,,
Pancreatitis	Rare (Cardell and Gurling, 1954)	Rare (Reifenstein *et al.*, 1939)
Pleurisy and pulmonary lesions	Fairly common (Reader *et al.*, 1951; Ellman *et al.*, 1951; Cardell and Gurling, 1954; Eadie and Thompson 1955)	Fairly common
Pericarditis and valvular lesions	Fairly common (Reader *et al.*, 1951; Ellman *et al.*, 1951; Cardell and Gurling, 1954)	,, ,,
Central nervous system involvement	Rare (Sheldon, 1939; Ramage and Kinnear, 1956)	Rare
Polyarteritis nodosa	Rare (Cardell and Gurling, 1954; Ramage and Kinnear, 1956)	,, (Lincoln and Ricker, 1954; Hill, 1957)

Note: Estimates of the frequency of the various features of Sjögren's syndrome are compiled from the literature and from my series. References are given only to little-known manifestations of systemic L.E. Extensive reviews of this disease are by Harvey *et al.* (1954) and Hill (1957).

TABLE IV.—*Clinico-pathological Features Common to Sjögren's Syndrome and S.L.E.*

	Sjögren's Syndrome	S.L.E.
Hypochromic anaemia	Common	Common
Leucopenia	Fairly common (Critchley and Meadows, 1933; Cadman and Robertson, 1952; Gurling, 1953; Thompson and Eadie, 1956)	Fairly common
Thrombocytopenia	Fairly common	,, ,,
Raised E.S.R.	Common	Very common
Lowered albumin	,,	Common
α_2-globulin raised	Fairly common	Fairly common
γ- ,, ,,	Common	Common
Thymol turbidity abnormal	,, (McLenachan, 1956)	,,
False positive W.R.	Rare (Coverdale, 1948)	Fairly common
Albuminurea	,, (Sjögren, 1943; Reader *et al.*, 1951)	,, ,,
L.E. cells	Fairly common	Very common

(Table I) had Mikulicz's disease, and L.E. cells were found in both cases. Therefore Mikulicz's disease is probably a form of systemic L.E.

Felty's Syndrome.—Gurling (1953) and Thompson and Eadie (1956) have reported cases of Sjögren's syndrome with Felty's syndrome, and two more are described in our series (Table I, Cases 14 and 24), one of which (Case 24) had L.E. cells present. The whole picture of Felty's syndrome—leucopenia, splenomegaly, and rheumatoid arthritis—fits that of systemic L.E.

Boeck's Sarcoid.—This has been reported in association with Sjögren's syndrome (Gruber, 1956; Ramage and Kinnear, 1956; Jones and Stevenson, 1957). It should be noted, however, that the skin lesions of sarcoid can easily be mistaken for those of chronic L.E. (Grund, 1950), and the radiological appearances of the chest in sarcoid and "lupus pneumonitis" are similar. Some cases of dry eyes may, however, be due to sarcoidosis, such as the case reported by Jones and Stevenson (1957), but these are more accurately named keratoconjunctivitis sicca and are probably rather rare. It is possible that sarcoidosis and systemic lupus are related (*British Medical Journal*, 1958); Teilum (1948) brackets the two diseases together as allergic hyperglobulinosis.

Sjögren's Syndrome and Lymphadenoid Goitre

The association of hypothyroidism, lymphadenoid goitre, and raised serum cholesterol with Sjögren's syndrome (Gifford *et al.*, 1943; Gruber, 1956; McLenachan, 1956) is interesting. There are striking similarities between lymphadenoid goitre and Sjögren's syndrome. Both are conditions which mainly affect middle-aged women, and the symptoms tend to fluctuate in intensity and to vary from time to time. The E.S.R. is often raised, the gamma-globulin increased, and flocculation tests (thymol turbidity) are abnormal. Cardell and Gurling (1954) noted the close resemblance between the histology of the salivary and lacrimal glands in Sjögren's syndrome and the thyroid in lymphadenoid goitre and the late stages of myxoedema. Infiltration of the glandular tissues with lymphocytes and plasma cells is found in the two conditions, as are lymphoid follicles, giant cells, atrophy of the glandular tissue, and fibrosis.

If the histological and clinical features of Sjögren's syndrome and lymphadenoid goitre are so similar then they may have aetiological factors in common. Riott *et al.* (1956) found that the serum of patients with lymphadenoid goitre contained an antibody to the patient's own thyroglobulin; and postulated that the destruction of the thyroid results from the progressive interaction of thyroglobulin in the gland with the auto-antibody present in the patient's circulation. A similar process therefore may be occurring in patients with Sjögren's syndrome: auto-antibodies being produced by some substance present in the lacrimal and salivary glands. Such a process might be expected in systemic lupus, in which there are gross disturbances in antibody mechanisms.

Summary and Conclusions

Clinical and pathological evidence is produced showing that Sjögren's syndrome, Mikulicz's disease, and Felty's syndrome are manifestations of systemic lupus erythematosus.

Of 28 patients with Sjögren's syndrome examined, 10 had L.E. cells in the peripheral blood and two of these had Mikulicz's disease and one Felty's syndrome.

Furthermore, it is noted that there are many resemblances between Sjögren's syndrome and lymphadenoid goitre, and it is suggested that they may have aetiological factors in common.

The clinical course of systemic lupus erythematosus may extend over many years, and at times the patient may be in apparent good health. During these periods of remission minor evidence of clinical activity, such as arthralgia, sensitivity to the sun, and chilblains, may be discovered. Most cases of Sjögren's syndrome reported in the literature are in this benign phase. Most published reports on cases of Sjögren's syndrome give only a brief cross-section in space–time of the natural history of the disease. A picture of the whole life-history of a number of cases of the syndrome, including necropsies, would, I feel sure, produce even more evidence that Sjögren's syndrome is a form of systemic L.E.

ADDENDUM.—Since this paper was written B. R. Jones (*Lancet*, 1958, **2**, 773) has demonstrated auto-antibodies in Sjögren's syndrome.

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REFERENCES

Beetham, W. P. (1935). *Trans. Amer. Ophthal. Soc.*, **33**, 413.
Brit. med. J., 1958, **2**, 784.
Bruce, G. M. (1941). *Arch. Ophthal. (Chicago)*, **26**, 945.
Cadman, E. F. B., and Robertson, A. J. (1952). *Brit. med. J.*, **2**, 68.
Cardell, B. S., and Gurling, K. J. (1954). *J. Path. Bact.*, **68**, 137.
Coverdale, H. (1948). *Brit. J. Ophthal.*, **32**, 669.
Critchley, M., and Meadows, S. P. (1933). *Proc. roy. Soc. Med.*, **26**, 308.
Dubois, E. L. (1956). *Ann. intern. Med.*, **45**, 163.
Eadie, S., and Thompson, M. (1955). *Brit. J. Ophthal.*, **39**, 90.
Ellman, P., Weber, F. P., and Goodier, T. E. W. (1951). *Quart. J. Med.*, **44**, 33.
Gifford, S. R., Puntenney, I., and Bellows, J. (1943). *Arch. Ophthal. (Chicago)*, **30**, 207.
Gruber, E. (1956). Ibid., **55**, 42.
Grund, J. L. (1950). *Arch. Derm. Syph. (Chicago)*, **61**, 20.
Gurling, K. J. (1953). *Ann. rheum. Dis.*, **12**, 212.
Haas, E. (1951). *Virchows Arch. path. Anat.*, **320**, 264.
Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H. (1954). *Medicine (Baltimore)*, **33**, 291.
Henderson, J. W. (1950). *Amer. J. Ophthal.*, **33**, 197.
Hill, L. C. (1957). *Brit. med. J.*, **2**, 655.
Holm, S. (1949). *Acta ophthal. (Kbh.)*, Suppl. 33.
Jones, B. R., and Stevenson, C. J. (1957). *Brit. J. Ophthal.*, **41**, 153.
Klemperer, P., Gueft, B., Lee, S. L., Leuchtenberger, C., and Pollister, A. W. (1950). *Arch. Path. (Chicago)*, **49**, 503.
Lincoln, M., and Ricker, W. A. (1954). *Ann. intern. Med.*, **41**, 639.
MacLean, K., and Robinson, H. S. (1954). *Canad. med. Ass. J.*, **71**, 597.
McLenachan, J. (1956). *Trans. ophthal. Soc. U.K.*, **76**, 413.
Morgan, A. D., and Raven, R. W. (1952). *Brit. J. Surg.*, **40**, 154.
Morgan, W. S. (1954). *New Engl. J. Med.*, **251**, 5.
—— and Castleman, B. (1953). *Amer. J. Path.*, **29**, 471.
Ramage, J. H., and Kinnear, W. F. (1956). *Brit. J. Ophthal.*, **40**, 416.
Reader, S. R., Whyte, H. M., and Elmes, P. C. (1951). *Ann. rheum. Dis.*, **10**, 288.
Reifenstein, E. C., Reifenstein, E. C., jun., and Reifenstein, G. H. (1939). *Arch. intern. Med.*, **63**, 553.
Riott, I. M., Doniach, D., Campbell, P. N., and Hudson, R. V. (1956). *Lancet*, **2**, 820.
Shearn, M. A., and Pirofsky, B. (1952). *A.M.A. Arch. intern. Med.* **90**, 790.
Sheldon, J. H. (1939). *Proc. roy. Soc. Med.*, **32**, 255.
Sjögren, H. (1943). *A New Conception of Keratoconjunctivitis sicca*. Australasian Med. Publishing Co., Sydney.
Teilum, G. (1948). *Amer. J. Path.*, **24**, 389.
Thompson, M., and Eadie, S. (1956). *Ann. rheum. Dis.*, **15**, 21.
Weber, F. P. (1945). *Brit. J. Ophthal.*, **29**, 299.
Wilkinson, M., and Sacker, L. S. (1957). *Brit. med. J.*, **2**, 661.

OUTBREAK OF ADENOVIRUS INFECTION IN THE PORTSMOUTH NAVAL COMMAND, 1958

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The Commission on Acute Respiratory Diseases of the United States Army (1946) postulated the existence of a special disease of the upper respiratory tract affecting chiefly young recruits during their first four weeks of military training. A virus agent was eventually isolated by Hilleman and Werner (1954) from cases of atypical pneumonia and acute respiratory disease, and found to be similar to a "masked" virus recovered from adenoid tissue removed at operation from young children (Rowe *et al.*, 1953).

Adenovirus infection in military recruits causes febrile upper respiratory catarrh with sore throat and cough. About half the patients develop an exudate on the tonsils, and up to 16% may show radiological evidence of pneumonitis (Hilleman, 1956). These infections are of great importance to American Service authorities, and their cost has been estimated at nine million dollars a year.

Outbreaks in this country have been reported from Army and R.A.F. establishments (Tyrrell *et al.*, 1956; Andrews *et al.*, 1956) and from residential schools (Kendall *et al.*, 1957).

The virus has at least seventeen serotypes (Rowe *et al.*, 1958), and to avoid confusion the term "adenovirus" was proposed to cover the group. Types 3, 4, and 7 are responsible for most military cases (Hilleman, 1956); types 1, 2, and 5 cause respiratory infections in young children; and types 6, 8, and 10 are mainly implicated in eye infections (*J. Amer. Med. Ass.*, 1957).

The outbreak reported here became manifest in the Portsmouth Naval Command in February, 1958. It was soon realized that this outbreak was larger than any previously reported from Service sources in this country, and it was decided to investigate its effect on the personnel in five of the larger establishments (A, B, C, D, and E).

Laboratory Methods

Paired sera were taken in the first ten days of illness and two weeks or more later. They were taken routinely from patients admitted to hospital with upper respiratory infections from January and from patients in sick quarters in centres A, B, and C from February until April.

Convalescent sera, taken after the first ten days of illness, were obtained from patients in centres A, B, C, D, and E. They were frozen until tested by complement-fixation against antigens of influenza A, B, and C, *Rickettsia burneti*, adenovirus, and the psittacosis–L.G.V. group of viruses described by Andrews *et al.* (1956).

These antigens were obtained from the Standards Laboratory for Serological Reagents, Colindale. The tests were performed in "perspex" plates of the type recommended for haemagglutination tests (W.H.O., 1953). 0.1 ml. each of serum dilution, antigen at optimal dilution, and complement (2½ M.H.D.) were mixed and incubated for 75 minutes at 37° C. 0.2 ml. of a 1% suspension of sensitized sheep erythrocytes was then added and incubated at 37° C. for a further 30 minutes, when the plates were cooled to 4° C., left overnight at that temperature, and read. The serum titre was the highest initial serum dilution which showed 75% or more red cells unlysed.

With paired sera a fourfold or greater rise in titre between the acute and convalescent samples was regarded as diagnostic. With a single convalescent serum, obtained from establishments where diagnostic rises in titre were found, a titre of 1 in 20 or greater was considered significant. Titres below 1 in 20 were regarded as negative.

Specimens of faeces, and throat swabs taken by a method similar to that described by Hawkins *et al.* (1956), were frozen. When required for testing, the specimens were thawed and 0.2 ml. of the fluid was inoculated into stationary HeLa cell tissue cultures in a maintenance medium comprising 0.5% lactalbumin in Hanks's buffered salt solution with added 4% fowl serum and enough penicillin and streptomycin to give a final concentration of 100 units of each per millilitre. The tubes were observed for seven days without change of medium or until degeneration occurred, and 0.2 ml. of the fluid was inoculated into fresh tubes and the process repeated until 21 days had elapsed.

Virus isolations were confirmed by complement-fixation tests, using the culture fluids as antigens and a known pool of positive human serum. Neutralization tests were performed in HeLa cell tissue cultures, using rabbit antisera prepared against adenovirus types 1 to 8.

Results

From 511 patients admitted to hospital between January and July 445 pairs of sera were obtained. An analysis of the laboratory findings in these patients is shown in Table I. In addition, 80 pairs of sera and 373 single convalescent sera were obtained from patients in centres A to E. All 525 pairs of sera were tested, and 201 were found to have rising titres against adenovirus. The distribution of these 201 rising titres is set out in Table II. The distribution of titres against adenovirus found in the 373 single convalescent sera is shown in Table III. In addition, over 900 sera taken from

TABLE I.—*Monthly Analysis of Laboratory Findings in Patients Admitted to Upper Respiratory Wards*, 1958

	Jan.	Feb.	Mar.	Apr.	May	June	July	Total
No. of patients admitted	80	111	127	67	51	32	43	511
Streptococcal and Vincent's infection ..	13	20	9	12	11	10	19	94
Glandular fever	1	2	—	3	4	1	2	13
No. of paired sera tested ..	61	103	126	57	39	29	30	445
Influenza A	22	8	—	2	—	—	—	32
Adenovirus	3	36	82	18	9	2	—	150
Influenza C	1	1	1	1	—	—	—	4
Influenza A and C ..	1	—	—	—	—	—	—	1
Influenza A and adenovirus	—	1	1	—	—	—	—	2
Q Fever	1	—	1	—	—	—	—	2
Negative	33	57	41	36	30	27	30	254

TABLE II.—*Distribution of Fourfold or Greater Rises in Titre Against Adenovirus Found in 201 of 525 Pairs of Sera Tested*

	<1/2–1/8	<1/2–1/16	1/2–1/8	1/2–1/16	1/4–1/16	<1/5–1/10	<1/5–1/20	<1/5–1/40 or Greater	1/5–1/20	1/5–1/40 or Greater	1/10–1/40 or Greater
January ..		1					1			1	
February ..	1		1	1	1	3	4	20	2	2	2
March ..	1	1	1	1		23	36	48	1	16	4
April ..						3	4	9	1	1	
May ..						2	2	4			1
June ..						1		1			
Total ..	2	2	2	2	1	32	47	82	4	20	7

TABLE III.—*Distribution of Titres Against Adenovirus Found in 373 Single Convalescent Sera*

C.F. Titre against Adenovirus ..	<1/10	1/10	1/20	1/40 or Greater	Total
No. of single convalescent sera ..	90	73	81	129	373
% of single convalescent sera ..	24	20	22	35	101

civilians in the area during this outbreak and 767 pairs of sera from this Command in 1957 were examined. Less than 5% of these had titres of 1 in 10 or greater.

Adenovirus type 3 was isolated from 3 of 40 throat swabs and 1 of 16 specimens of faeces taken in the first three days of illness from patients subsequently found serologically to have had adenovirus infection.

Seven patients with streptococcal or Vincent's infection were also serologically positive for adenovirus.

Nearly all the patients admitted to hospital complained of sore throat and cough and were febrile. They appeared more distressed than those seen in the previous six months, when an outbreak of influenza A had occurred (Fraser *et al.*, 1958).

For 132 consecutive cases of serologically proved adenovirus infection the average stay in hospital was 8.1 days, as compared with 5.2 days for the influenza outbreak. The average age of the patients was 19 years, with extremes of 16 and 39, and the average length of service in the Navy was 1 year and 9 months, with extremes of 1 month and 15 years. An analysis of their symptoms and complications is given in Table IV.

TABLE IV.—*Analysis of Clinical Findings in 132 Consecutive Cases of Confirmed Adenovirus Infection*

Total cases	132
Sore throat	129 (98%)
Cough	95 (73%)
Exudate on tonsils	17 (13%)
Clinical pneumonia	8 (6%)
Radiological evidence of pneumonitis on discharge	7 (5%)
Gastro-enteritis	7 (5%)
Stevens-Johnson syndrome	2 (1%)

One case of otitis media and one of sinusitis were seen. Two patients had angina and ulceration of the mouth and eventually progressed to the full picture of the Stevens–Johnson syndrome. Despite extreme chemosis of the conjunctivae there was no photophobia or corneal scarring. Resolution was complete in both patients.

During the investigation 4 out of 12 cases of pneumonia admitted to the general medical wards were proved to be adenovirus infections. Three of eight cases of suspected tuberculosis found by mass miniature radiography were also shown to have adenovirus infections.

The ward routine and treatment were unchanged from the influenza outbreak of 1957, previously mentioned (Fraser *et al.*, 1958). As before, antibiotics were given only for complications. The two cases of Stevens–Johnson syndrome were treated with cortisone and oxytetracycline, and after a week on this treatment nystatin was added to suppress a superimposed monilial infection.

The 511 patients admitted to hospital between January and July suffering from febrile upper respiratory illnesses came from all parts of the Command.

Centres A to E largely represent the different living conditions and drafting arrangements found in the

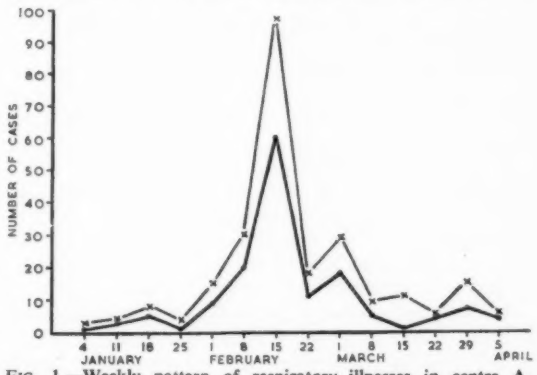

FIG. 1.—Weekly pattern of respiratory illnesses in centre A. Number of fresh cases reported to Saturday of each week. ×——×, Acute respiratory disease. ●——●, Serologically confirmed cases of adenovirus infection.

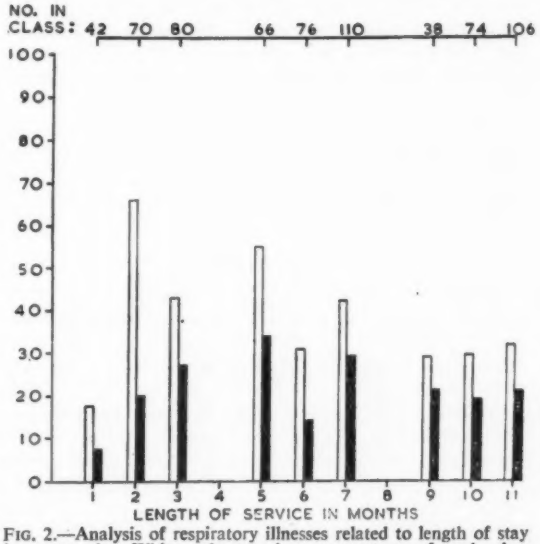

FIG. 2.—Analysis of respiratory illnesses related to length of stay in centre A. White columns show percentage of each class attacked by acute respiratory disease (all forms). Black columns show percentage of each class attacked by adenovirus infection, as determined serologically.

Command. It was possible to obtain records of those reporting sick with acute respiratory disease in each of them, and, as already stated, a further 80 paired sera and 373 single convalescent sera were taken and tested.

Centre A was a boys' training establishment where recruits joined in groups at about five-weeks intervals. They remained together for the first few weeks and subsequently mixed with the older residents. Their ages ranged from 15 to 16 years. Of 662 boys at risk during the spring term (January to March), 262 had an upper respiratory infection, 149 of these cases being considered serologically to be due to adenovirus.

Upper respiratory illnesses accounted for 1,301 days' sickness, 825 of which were thought to be due to adenovirus infection. The number of patients with respiratory illnesses who reported each week at Centre A is shown in Fig. 1.

Adenovirus infection in military life has hitherto been regarded as a hazard of the very new recruit (Hilleman, 1956). Fig. 2 shows the incidence of infection related to the length of stay in this recruit centre. It is seen that length of service up to 12 months had no apparent effect on the proportion of patients suffering from adenovirus infection.

Centre B has several courses of training, and each course remains as a unit for up to several years although there is a common meeting-ground in the canteen and cinema.

In one group of 379 there were 56 upper respiratory infections, of which 47 were found serologically to be due to adenovirus. In another group of 602, of 84 cases of infection 55 were shown to be due to adenovirus. Upper respiratory infections accounted for 666 days' sickness, of which 470 were due to adenovirus.

Centre C takes young men from other establishments for specialized training. During the quarter, 86 upper respiratory infections were reported, of which 41 were found serologically to be due to adenovirus. Upper respiratory infections accounted for 458 days' sickness, of which 261 were due to adenovirus.

Centre D is a ship where, during March, 23 of 42 upper respiratory infections were considered serologically to be due to adenovirus. Upper respiratory infections caused 234 days' sickness, of which 146 were due to adenovirus.

Centre E holds several short training courses, and there is considerable movement of personnel in and out of the establishment. Serological evidence of adenovirus infection was found in 20 out of 28 cases examined.

Discussion

Although adenoviruses can be isolated from about half the tonsils and adenoids removed surgically from children (Rowe *et al.*, 1953), they appear to cause little respiratory illness in the civil population. In a study of respiratory infections in families (Jordan *et al.*, 1956) very few cases were found. Similar results were obtained from a student health service (Evans, 1957). Outbreaks of moderate severity have occurred in residential schools, but, in general, adenovirus infections have been regarded as diseases of the Services, particularly of recruit units.

From Table I it will be seen that influenza in this Command had abated by the end of February. The adenovirus outbreak which began in February lasted until June. Most cases were seen in February and March.

The appearance of several foci of adenovirus infection within a short period of time suggested that the outbreak had arisen *de novo*; however, examination of the hospital records for 1957 showed that fourfold or greater rises in titre were found in 5 out of 767 pairs of sera tested. Although this suggests that the infection may have been present in latent form, it is not justifiable to assume that the same type was responsible for the sporadic cases in 1957 and the large numbers of cases this year, since no virus was isolated until the present outbreak.

The figures obtained from centres A to E represent bed cases only. Since many patients were treated as ambulant cases or at home these figures underestimate the real incidence by about a half, as suggested by the numbers treated on the attending list.

This outbreak did not seem to follow the pattern reported in the U.S. Armed Forces (Hilleman, 1956), in that infection was widespread throughout the Command and cases occurred in all age groups of a predominantly young population. It did, however, resemble that described by Munro-Ashman *et al.* (1958) in that, although type 3 adenovirus was presumed to be the cause in both, conjunctivitis was seldom seen. No similar outbreaks were reported from the rest of the country during the period.

As reported above, examination of 767 pairs of sera from this Command in 1957 and over 900 civilian sera from this area during the outbreak showed that a titre of 1 in 10 or greater against adenovirus occurred in less than 5%. It was in view of this that titres of 1 in 20 or greater in single convalescent sera were considered significant if obtained from centres where fourfold or greater rises in titres had also been found.

The low isolation rate of the virus from throat swabs and faecal specimens may have been due to the storage of samples above −20° C., which may have led to loss of virus. Medication of the throats with gargles four hours before sampling may have had a similar effect. Subsequent tests with the strains from this outbreak did not indicate that the maintenance medium was inhibitory.

Summary

The influenza A (Asian) epidemic of 1957 in this Command ended in February, 1958. It was followed by a widespread outbreak of adenovirus infection.

The chief symptoms were febrile sore throat with cough. Of 525 patients whose paired sera were tested, 201 showed fourfold or greater rises in titre, and evidence of recent infection was found in 210 of 373 patients whose single convalescent sera showed titres of 1 in 20 or greater. Adenovirus type 3 was isolated from throat swabs of three patients and from the faeces of another.

We are indebted to the Medical Director-General of the Navy for permission to publish and to Professor A. Bradford Hill for statistical advice. The following medical officers kindly supplied clinical notes and blood specimens: Surgeon Captain S. H. R. Price, Surgeon Commanders G. N. Shell and C. M. Lamont, and Surgeon Lieutenant Commander G. A. R. Giri. Sick Berth Petty Officer J. E. Goodings prepared the Charts and the Tables.

REFERENCES

Andrews, B. E., McDonald, J. C., Thorburn, W. B., and Wilson, J. S. (1956). *Brit. med. J.*, **1**, 1203.
Commission on Acute Respiratory Diseases (1946). *Amer. J. publ. Hlth*, **36**, 439.
Evans, A. S. (1957). *New Engl. J. Med.*, **256**, 377.
Fraser, P. K., Hatch, L. A., and Hughes, K. E. A. (1958). *J. roy. nav. med. Serv.*, **44**, 285.
Hawkins, G. F. C., Hatch, L. A., and McDonald, J. C. (1956). *Brit. med J.*, **2**, 1200.
Hilleman, M. R. (1956). *U.S. armed Forces med. J.*, **7**, 1717.
—— and Werner, J. H. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **85**, 183.
Jordan, W. S., Badger, G. F., Curtiss, C., Dingle, J. H., Ginsberg, H. S., and Gold, E. (1956). *Amer. J. Hyg.*, **64**, 336.
J. Amer. med. Ass., 1957, **163**, 40.
Kendall, E. J. C., Riddle, R. W., Tuck, H. A., Rodan, K. S., Andrews, B. E., and McDonald, J. C. (1957). *Brit. med. J.*, **2**, 131.
Munro-Ashman, D., Gardner, P. S., Taylor, C. E. D., and McDonald, J. C. (1958). *Lancet*, **2**, 121.
Rowe, W. P., Hartley, J. W., and Huebner, R. J. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **97**, 465.
—— Huebner, R. J., Gilmore, L. K., Parrott, R. H., and Ward, T. G. (1953). Ibid., **84**, 570.
Tyrrell, D. A. J., Balducci, D., and Zaiman, T. E. (1956). *Lancet*, **2**, 1326.
World Health Organization (1953). *Techn. Rep. Ser.*, No. 64. Geneva.

ANTIBODIES TO ASIAN INFLUENZA AND INFLUENZA B: EDINBURGH, 1958

BY

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The pandemic of Asian influenza reached England in August, 1957, and spread to the north by September. In Scotland experience of the infection was heavy, as is shown by returns of the Regional National Insurance Offices for increased claims for sickness benefit during that period. A baseline for claims is estimated on the average for the months from April to December of the previous year, and any rise of more than 250% over that baseline or of more than 30% over the previous week is considered significant. There was a marked general increase in claims throughout the country over the weeks from September 10 to November 5. During this time the figures in Scotland peaked to 613% over the baseline, N.W. England being next with 526%, and S.W. England with 525% (Brunyate, 1958).

It was of interest, therefore, to estimate by means of haemagglutination inhibition tests the level of antibodies against the Asian influenza virus in a cross-section of the population living in the Edinburgh area. Information about the extent of the infection in the community during the epidemic in the autumn of 1957 would make it possible to assess the level of susceptibility should a second wave occur in the spring of 1959. At the same time the collected sera were tested for antibody titre against influenza B virus which had been responsible for an epidemic in Edinburgh in December, 1954.

Materials and Methods

Sera.—For our purpose it was felt that sera from blood donors would be reasonably representative of the adult community. These were collected for us through the courtesy of the Blood Transfusion Service (S.E. Scotland). The bacteriology department of the Royal Infirmary, Edinburgh, supplied sera from the antenatal clinics and V.D. department and from patients in the medical and surgical wards. Small numbers of sera were also obtained from the City Fever Hospital and from general practitioners. Our aim was to collect 100 samples of sera (50 male, 50 female) in each 5-year age group from birth to 80 years of age during August and September, 1958. For the ages between 16 and 60 this was easily accomplished, but below and above these ages only a proportion of the numbers aimed at was achieved. In addition to the samples from the general community, specimens of sera were collected from nursing staff whose histories regarding Asian influenza were known and from cases of chronic bronchitis, many of whom had been under medical supervision during the previous year.

Treatment.—The sera were stored at −30° C. until required. To prevent bacterial contamination, penicillin and streptomycin were added to them (1,000 units of each per ml. of serum approximately). Before use the sera were treated with potassium metaperiodate (KIO_4) to remove non-specific inhibitors (Svedmyr, 1949; Lim *et al.*, 1957).

Virus.—Two strains of influenza virus were used—namely, Asian influenza A/England/341/57 isolated in our own laboratory, and influenza B (Lee). The antigens were prepared from the allantoic fluid of 11-day-old chick embryos.

Haemagglutination inhibition tests were carried out by a modification of the World Health Organization's plastic plate technique (Lépine, 1954). 0.2 ml. of virus containing four haemagglutinating doses was added to 0.2 ml. of serum, and to this was added 0.2 ml. of a 0.25% suspension in saline of fowl R.B.C.s. The titres of the sera were expressed as the reciprocals of the highest dilution of serum giving *complete inhibition* of haemagglutination. The lowest dilution of serum used was 1:8. The usual controls were set up with each batch of sera tested.

Results

The results are given (1) as the percentage experience of infection as gauged by the proportion with positive sera in a dilution of 1:8 or over; and (2) as the arithmetic means of the reciprocals of the antibody titres for each age group (Tables I and II, Figs. 1 to 4). The graphs for the percentages with demonstrable antibody in each age group fit reasonably well into those showing the average titre distribution. Results were calculated separately for men and for women, as it was thought that there might be a difference in experience of infection due to sex or environment. No significant difference between the two sexes was found.

Apart from the special groups of nurses and chronic bronchitics, 1,187 sera were examined for antibodies to Asian influenza virus A, and positive haemagglutination inhibition tests were obtained in 413, or 34.8%, with a range of from 14 to 69% in the different age groups.

The findings (Table I; Figs. 1 and 2) of the percentage experience and of antibody titre to Asian influenza virus show a high level in the younger age groups (0–15 years), although the total number of children in these age groups is small. However, the data correspond with the evidence that the incidence of influenza is at all times highest in the younger age groups (Hennessy, Davenport, and Francis, 1955). Thereafter the antibody titre falls to almost its lowest level between 25 and 40

years of age and rises again between 40 and 60, only to fall away once more in the oldest age groups.

For influenza B, 1,182 sera were examined. Positive haemagglutination inhibition tests occurred in 1,076, or 91% of these, with a range from 48 to 98% in the different age groups. In contrast to the antibody findings with Asian influenza virus A, the data (Table II; Figs. 3 and 4) for percentage experience and arithmetic mean of the antibody titres show that the levels are low in childhood (0–15 years), rise rapidly in adolescence, and remain as a high plateau until they dip slightly from age 50 onwards.

Sera from 96 nurses were examined. In the group of 87 who had received no vaccine, 35 gave a history of influenza and had an average antibody titre against Asian influenza of 91, with an experience of 80%, while 52 who had no history of Asian influenza had an average antibody titre of 37 but with a high general experience of infection (54%). There appears, therefore, to have been a considerable amount of symptomless infection amongst the nurses.

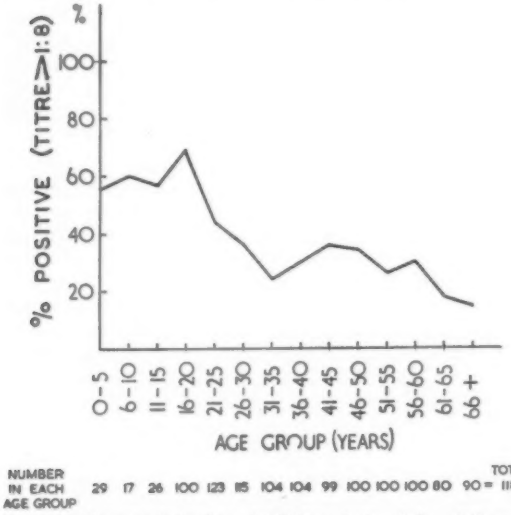

FIG. 1.—Haemagglutination inhibition tests—Asian influenza. Civilian population experience (average=34.8%).

Discussion

It is interesting to compare our results for antibody titre against Asian influenza virus in sera collected in Edinburgh during August and September, 1958, with those of Clarke *et al.* (1958). They used cholera vibrio filtrate to neutralize non-specific inhibitor in their sera collected in the North of England in November, 1957, and expressed their antibody titres as the reciprocal of the initial dilution of serum producing *partial inhibition* of haemagglutination. They obtained

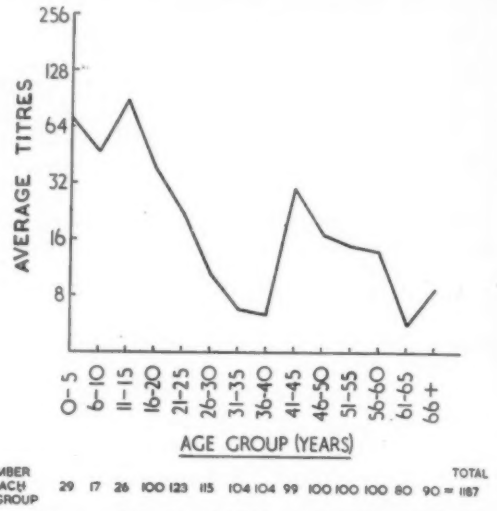

FIG. 2.—Haemagglutination inhibition tests—Asian influenza. Arithmetic mean time (average=20.3).

283 (44%) of positives out of 637 sera tested, with a sharp fall from 71% at 10–19 years to 46 and 40% in the 20–29 and 30–39 age groups respectively. The curves of percentage experience and average antibody titre are thus very similar to those shown in our graphs, though the average antibody titre in the Sheffield survey runs at a lower level. The results are not strictly comparable because of the different criteria adopted for the reading of the haemagglutination inhibition tests and of the difference in age grouping.

A similar fall in titre to P.R.8 and F.M.1 strains of influenza virus A was noticed by Hennessy, Davenport, and Francis (1955). They found a peaking of antibodies to those strains at 16–20 years of age, with a marked decline in the frequency of antibody between 25 and 29 years of age. On the other hand, Hilleman *et al.* (1954, 1958) found a high antibody titre to both P.R.8 and F.M.1 in this age group.

Influenza B has been prevalent in Britain since 1945, and, though normally it tends to be more an endemic disease than influenza A, it occasionally initiates very

TABLE I.—*Asian Influenza C.I.H. Post-epidemic Sera Tested Against A/England/341/57*

Mean*	69·0	56·5	93·2	40·6	23·7	12·0	6·4	5·9	30·2	17·4	15·3	14·4	4·0	9·7	Total
H.I. titre:															
1,024 ..			1						1						2
512 ..			1	1	1	1						1			5
256 ..	5	2	1	4	4				4	3	2	1		1	27
128 ..	5	2	3	6	2		1	1	3	2	5	1		3	34
64 ..	3	1	1	14	6	4	1	1	1	4	1	1	2	1	41
32 ..	2	3	4	13	13	6	9	5	8	7	5	9	3	4	91
16 ..	1	2	3	25	16	21	8	12	11	11	6	7	3	1	127
8 ..			1	6	13	10	7	8	8	7	7	10	6	3	86
<8 ..	13	7	11	31	68	73	78	77	63	66	74	70	66	77	774
No. positive	16/29	10/17	15/26	69/100	55/123	42/115	26/104	27/104	36/99	34/100	26/100	30/100	14/80	13/90	413/1,187
% ..	55·2	58·8	57·7	69	44·7	36·5	24	30	36·4	34	26	30	17·5	14·4	34·8
Age group	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66+	

*Arithmetic mean of sera with titres of 8 or more.

large epidemics (Andrewes, 1954). Such an epidemic occurred in Edinburgh in December, 1954. The North of England had similar epidemics about this time. The high titres to influenza B in the adult population reflect the widespread exposure of the population to the virus and the resultant high immune state. Children, on the other hand, are mostly susceptible.

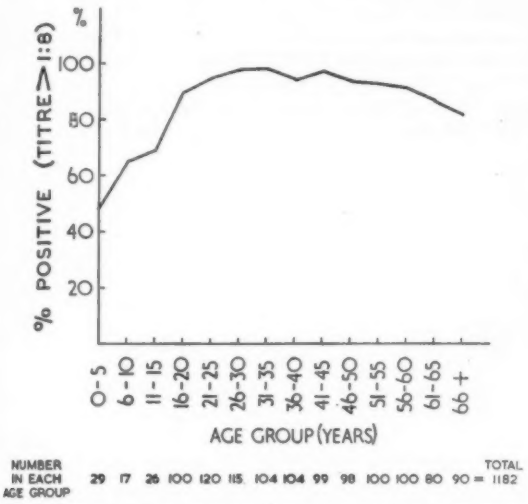

FIG. 3.—Haemagglutination inhibition tests—influenza B (Lee). Civilian population experience (average=91.0%).

From our results it would appear that the economically important age group between 25 and 40 are not well protected against Asian influenza and would be vulnerable in the event of a further epidemic of it. There are, however, a fair proportion of the sera which, though they do not give complete inhibition of haemagglutination at the lowest dilution tested, probably do contain some specific antibody as shown by partial haemagglutination inhibition. Individuals with such a basal immunity might respond well to a single boosting dose of vaccine, and this might be a useful precautionary measure for those in key positions in public services (transport, post office, police, etc.) and for nursing staff and doctors (Holland *et al.*, 1958).

Since this work was completed our attention has been drawn to the work of Choppin, Osterhout, and Tamm (1958), who described the differences of sensitivity of various strains of the Asian influenza virus both to haemagglutination inhibitor and neutralizing antibodies and to the action of the non-specific (Francis) inhibitor. The strain which we employed is insensitive to its non-specific inhibitors, and in preliminary tests appears to be rather less sensitive to the haemagglutination-inhibiting antibody than the R.I.5 strain described by these workers. It may be, therefore, that our results express something of an underestimate of the immune state of the population sampled.

Summary

Antibodies against Asian influenza were detected in 413 (34.8%) of 1,187 sera examined and against influenza B (Lee) in 1,076 (91%) of 1,182 sera examined.

The antibody titre to Asian influenza was highest in the 11–15 years age group and almost at its lowest in the economically important 25–40 years age group. By contrast, the antibodies to influenza virus B were very low in children and rose to a high plateau in adults.

In view of these findings vaccination against Asian influenza of adults in key positions might be advisable. Since in the age range 20–40 years many already have evidence of a low basal immunity, a single boosting dose of vaccine might be adequate.

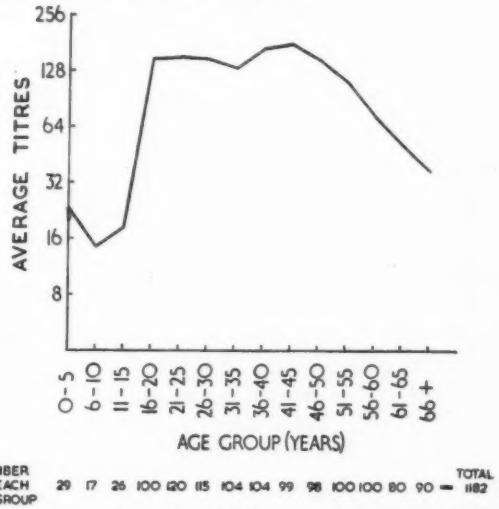

FIG. 4.—Haemagglutination inhibition tests—influenza B (Lee). Arithmetic mean time (average=123.4).

There appeared to be no significant difference in the experience of infection by men and women in the same age group.

We are indebted to Dr. Purnell W. Choppin, of the Rockefeller Institute, New York City, for the R.I.5 strain

TABLE II.—*Post-epidemic Asian Influenza Sera Tested Against Influenza B (Lee) Virus*

Mean*	24·8	15·1	18·8	150·6	158·2	148·7	133·2	178·9	192·5	150·2	116·2	78·1	53·5	39·2	Total
H.I. titre:															
1,024 ..				2	1			2	1	2					8
512 ..				9	13	15	8	17	16	10	8	5	2	1	104
256 ..	1			17	24	16	18	9	20	14	15	8	3	1	146
128 ..	2			18	20	23	22	28	25	14	11	8	5	3	179
64 ..			1	17	24	25	25	25	16	22	22	18	15	23	233
32 ..	3	6	10	15	21	17	19	8	13	19	20	19	18	18	206
16 ..	6	3	6	10	8	14	6	5	4	7	12	19	13	14	127
8 ..	2	2	1	3	3	2	3	4	2	6	5	14	13	13	78
<8 ..	15	6	8	9	6	3	3	6	2	4	7	9	11	17	106
No. positive	14/29	11/17	18/26	91/100	114 120	112/115	101/104	98/104	97/99	94/98	93/100	91/100	69/80	73/90	1,076/1,182
% .	48	64·7	69·2	91	95	97·4	97·1	94·2	98	95	93	91	86·3	81	91
Age group	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66+	

*Arithmetic mean of sera with a titre of 8 or more.

of Asian influenza virus. We also thank Dr. J. H. Bowie, Dr. R. A. Cumming, Dr. P. N. Edmunds, Dr. A. Joe, Dr. R. Lees, Dr. J. M. Murdoch, and Dr. R. E. Verney, for their co-operation in supplying the sera used for these tests. It is a pleasure also to mention the willingness with which the nursing staff volunteered their own sera for examination in this survey.

REFERENCES

Andrewes, C. H. (1954). *Wld Hlth Org. Monogr. Ser.*, **20**, 9.
Brunyate, W. D. T. (1958). *Roy. Soc. Prom. Hlth J.*, **78**, 545.
Choppin, P. W., Osterhout, S., and Tamm, I. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **98**, 513.
Clarke, S., Heath, R. B., Sutton, R. N. P., and Stuart-Harris, C. H. (1958). *Lancet*, **1**, 814.
Hennessy, A. V., Davenport, F. M., and Francis, T. (1955). *J. Immunol.*, **75**, 401.
Hilleman, M. R., Flatley, F. J., Anderson, S. A., Luecking, M. L., and Levinson, D. J. (1958). *New Engl. J. Med.*, **258**, 969.
—— Werner, J. H. and Gauld, R. L. (1954). *Wld Hlth Org. Monogr. Ser.*, **20**, 25.
Holland, W. W., Isaacs, A., Clarke, S., and Heath, R. B. (1958). *Lancet*, **1**, 820.
Lépine, P. (1954). *Wld Hlth Org. Monogr. Ser.*, **20**, 87.
Lim, K. A., Smith, A., Hale, J. H., and Glass, J. (1957). *Lancet*, **2**, 791.
Svedmyr, A. (1949). *Brit. J. exp. Path.*, **30**, 254.

GIANT INNOCENT GASTRIC ULCER

ITS BEHAVIOUR AND TREATMENT

BY

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Various writers have drawn attention to the giant innocent gastric ulcer (Lumsden, 1950; Marshak *et al.*, 1953; Reid, 1954; Jennings and Richardson, 1954). They have reported series of cases refuting the previously held belief that most gastric ulcers with a diameter of 3 cm. or more are malignant. Avery Jones (1957) has gone further in stating that gastric ulcers of a diameter of more than 3 cm. radiologically are much more likely to be simple than malignant.

Present Investigation

These giant ulcers often present a very atypical clinical picture and seriously endanger the life of the patient in spite of their "innocent" character. A study of a series of 73 giant ulcers has been undertaken to learn about their behaviour and how they should be treated. As in previous writings, the term "giant" is used to describe ulcers of which one diameter, either on the radiological film or in the surgical or necropsy specimen, is 3 cm. or more. This series, the largest yet recorded, is from the Gastro-enterological Unit of Whittington Hospital, where the patients have been under the care of Mr. W. W. Davey and Dr. T. St. M. Norris, to whom I am indebted for permission to report these cases. The patients presented during the period 1950–7.

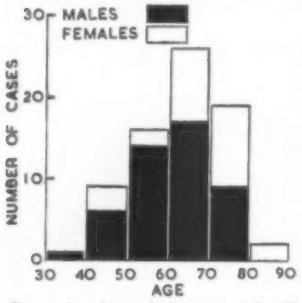


FIG. 1.—Age incidence of 73 patients with giant gastric ulcers.

Sex and Age Incidence.—The series consists of 47 males and 26 females, a ratio of 1.8:1. This conforms roughly with the ratio of 2:1 which applies to gastric ulcers in general (Illingworth, 1956). Fig. 1 shows the age incidence, being the age at which the patients presented at hospital with giant ulcers. It will be seen that the highest incidence is between 60 and 70, which is 20 years later than the highest incidence for gastric ulcers as a whole (Illingworth, 1953). The maximum incidence for males is also between 60 and 70, but that for females is between 70 and 80.

Size and Situation of Ulcers.—Table I shows the size of the ulcers, measured either radiologically or from the specimens. They have been situated mostly in relation to the lesser curve and the adjacent posterior wall of the stomach between the angulus and the cardia. In 80% of cases the ulcer penetrated the pancreas and in a further 10% it was adherent to it. Some ulcers have been entirely on the posterior wall and a few have been confined to the anterior wall. In a third of the cases the ulcer "saddled" the lesser curve. In the "saddle" type the anterior limb has frequently been adherent to the liver, while the posterior limb has penetrated the pancreas. Fig. 2 shows a large "saddle" ulcer which at operation measured 5 by 10 cm.

TABLE I

Size of Ulcers	Cases	
	Male	Female
3– 3·9 c.m.	24	13
4– 4·9 ,,	13	4
5– 5·9 ,,	4	6
6– 6·9 ,,	2	2
7– 7·9 ,,	0	1
8– 8·9 ,,	1	0
10–10·9 ,,	3	0
	47	26

Length of Gastric History.—Except in a few cases it has not been possible to determine how long the patient has had a giant ulcer and so decide whether it is a new one or merely the latest ulcer in a peptic ulcer history. An arbitrary division of the patients has been made into two groups: 29 (40%) had their gastric trouble for a year or less and 44 (60%) for over a year. The women were equally divided between the two groups, but two-thirds of the men had their gastric symptoms for more than a year and only one-third for less. Ten men had evidence of previous duodenal ulcers in addition to their giant gastric ulcers. Of these, nine were in the "over one year" group, suggesting that a duodenal ulcer was responsible for their early symptoms.

FIG. 2.—Large "saddle" ulcer which measured 5 by 10 cm. at operation.

Factors of Possible Aetiological Significance

Jennings and Richardson (1954) mentioned possible aetiological factors in the production of giant ulcers,

including irritation of the colon by constipation and aperients, alcohol, smoking, psychological factors, and chronic bronchitis. There was no evidence in this series that constipation or regular excessive consumption of alcohol were causative factors.

Smoking.—Out of 66 patients for whom information is available, 11 may be classed as heavy smokers (25 or more cigarettes a day). The ulcer of the only woman in this group has remained healed for five years although she still smokes 20 cigarettes a day. A man whose ulcer has remained healed for four years smokes 40–50 cigarettes a day. Eight patients have been treated by surgery, and the eleventh in the group died from carcinoma of the larynx with his ulcer unhealed. No conclusions can be drawn from these figures regarding the effect of heavy smoking.

Psychological Factors. — Obvious abnormal psychological factors were present in 10 out of the 73 patients. Five had anxiety states and a sixth patient developed her ulcer five years after a leucotomy. In only one patient in this group has the ulcer remained healed.

Chronic Bronchitis.—Sixteen patients had chronic bronchitis. The ulcers of 11 were treated medically and seven of them healed, but only one (Case 51 ; Fig. 5) has remained healed.

Gastric Mucosa.—Tanner (1954) has pointed out that in cases of gastric ulcer the gastric mucosa is occasionally well developed but much more often it is thinner than normal. He said that it appears that gastric ulcer frequently arises in a diseased or degenerate mucosa. This does not seem to be true for the giant gastric ulcer. In 43 cases there are notes about the quality of the mucosa, seen either in the gastrectomy specimen or through the gastroscope. In only four cases (9%) was it noted to be atrophic, in 17 (40%) it was hypertrophic, and in 22 (51%) it was average in quality. These figures suggest that the giant gastric ulcer arises more often in a well-developed mucosa than in a degenerate one.

Modes of Presentation of the Giant Ulcer

Table II shows the mode of presentation of the 73 cases. It will be seen that 41 (56%) presented with pain as the principal symptom and 25 (34%) with haemorrhage.

TABLE II.—*Modes of Presentation of the Giant Ulcer*

Haemorrhage	25
Pain	27
Pain and vomiting	12
Pain and abdominal tumour	2
Vomiting from gastric retention	3
Perforation	3
Loss of appetite and anaemia	1

Site of Pain.—Pain was a symptom in 70 out of the 73 patients and information about its site is available in 68. Of these 68, 49 (72%) had pain somewhere in the area of the epigastrium, the lower retrosternal region, the left hypochondrium, and the left lower chest. Pain was confined to the left lower chest in three patients, to the left iliac fossa in three, to the right iliac fossa in two, and to the hypogastrium in six. Thus in 14 patients (20%) the pain was not in the usual gastric area. Its gastric origin may be still more difficult to recognize if there is no food relationship, as occurred in about 20% of patients in this series. Diagnosis is thereby delayed, possibly dangerously if a haematemesis provides startling evidence of the site of the lesion.

Back Pain.—As already noted, in 90% of cases the ulcer either penetrated the pancreas or was adherent to it. In view of this it is surprising that only 34 (56%) out of 61 patients for whom there is information had back pain.

Complications of the Giant Gastric Ulcer

Haemorrhage

Of the 73 giant ulcers, 25 (34%) presented with haemorrhage ; another patient, who had been treated medically, was readmitted for this reason. In addition, seven patients had severe degrees of anaemia. Of the 26 patients with haemorrhage, only five (20%) ceased bleeding under conservative treatment and 21 (80%) required emergency surgery. The proportion requiring emergency surgery is, of course, much higher than that for haemorrhage from gastric ulcers in general. A high proportion of these giant ulcers penetrate to outside the stomach wall, and when that happens violent bleeding can occur from involvement of the splenic or left gastric arteries or their main branches.

Surgical Treatment.—Table III shows the emergency operations that were done on the 21 patients whose haemorrhage was treated surgically. Two operations

TABLE III.—*Emergency Operations for Haemorrhage*

	Cases	Deaths
Partial gastrectomy	18	4
Laparotomy only	2	2
Gastrotomy and undersewing	2	1

were done on one patient. Her general condition permitted only gastrotomy and undersewing of the vessel at the first operation. Four days later, when further bleeding occurred, a gastrectomy was successfully performed. Her posterior ulcer measured 5 by 5 cm.

Mortality.—It will be seen that 7 out of 21 patients died following emergency surgery. In the partial gastrectomy group, two died from leaks of the anastomosis, one died two months after operation from bronchial carcinoma, and the fourth, a diabetic of 79, died suddenly five days after operation. Of the two patients who had laparotomy only, one had massive secondaries in the liver from a bronchial carcinoma and the other died at the end of an operation under local analgesia in which his ulcer was not found. He was extremely obese and his ulcer was situated 3 cm. from the oesophagus. The remaining death occurred after an unsuccessful attempt to save an exsanguinated woman of 74 by aortic transfusion and undersewing of the vessel. The true mortality from haemorrhage in this series was 27%—7 deaths out of 26 patients treated for it. Haemorrhage from a giant gastric ulcer is often an exceedingly dangerous complication, occurring as it does in elderly patients who are not infrequently in poor general condition. Referring to massive haemorrhage from ulcers, Tanner (1954) has said that in some cases death is almost certain unless a hazardous gastrectomy is performed on a near moribund patient. A high operative mortality must therefore be accepted if lives are to be saved.

Perforation

Perforation is uncommon, as only about one-third of the ulcers involve the anterior wall of the stomach. Five cases in the series perforated—an anterior ulcer in three and the anterior limb of a " saddle " ulcer in two. There was one death (Case 39, Fig. 3). As this patient's ulcer had caused gastric retention before perforating, an

emergency gastrectomy was done. He died at the end of the operation and the necropsy finding was coronary occlusion.

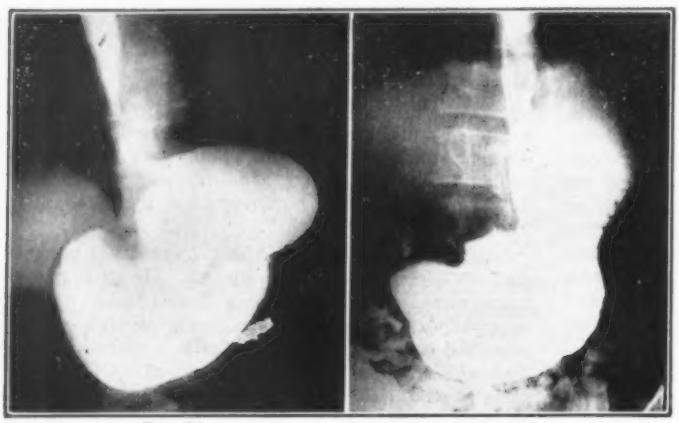
Gastric Retention

It is not generally realized that a large gastric ulcer situated low on the lesser curve can cause gastric retention with a big dilated stomach. The symptoms produced are similar to those of stenosing duodenal ulcer. Case 39 (Fig. 3), referred to above, is an example of this process.

There is a second way in which gastric retention occurs. Recurrent ulceration of the lesser curve causes progressive shortening of the lesser curve due to breakdown of tissue and healing by fibrosis. The length of the lesser curve between the oesophagus and the pylorus gets steadily less and there is relative elongation of the greater curve. As a result the stomach does not empty normally. Case 31 (Fig. 3) is an example of this process of shortening of the lesser curve.

Hour-glass Deformity

Two women and one man with giant ulcers developed hour-glass deformities of the stomach. It is unusual to get this deformity in a man.



Case 31. Case 39

FIG. 3.—Two giant ulcers that produced gastric retention. Case 39, a low lesser curve ulcer. Case 31, recurrent ulceration causing extreme shortening of the lesser curve.

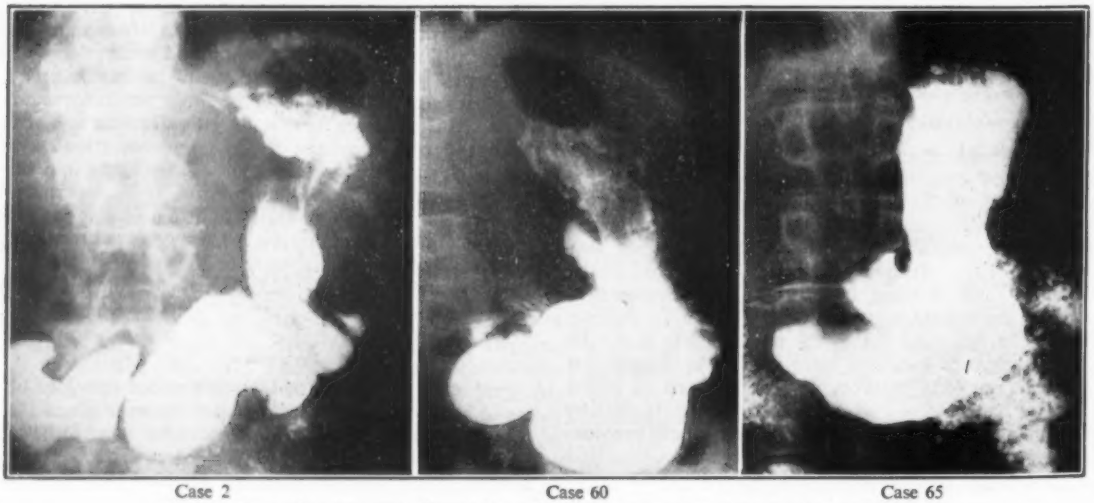
Diagnosis

In addition to stating that gastric ulcers of more than 3 cm. radiological size are much more likely to be simple than malignant, Avery Jones (1957) has said that the gastric ulcer which projects clearly from the lesser curve between the angulus and the cardia is virtually never malignant. On the other hand, mentioning size as one of the points to be considered in deciding whether a gastric ulcer is simple or malignant, Cochrane Shanks and Kerley (1958) have written: "Any ulcer larger than 2.5 cm. in diameter should be suspected as malignant until it has been proved to be simple. The larger the ulcer the greater should be the suspicion. Many large ulcers will, in fact, turn out to be simple but the maxim is none the less a sound one." The maxim would not appear to be a sound one for ulcers between the angulus and the cardia, as the evidence of this series shows.

During the period in which these 73 cases of giant innocent gastric ulcers presented for treatment, only two giant malignant ulcers of the lesser curve were seen. One was diagnosed as a malignant ulcer by gastroscopy. The other was thought to be innocent on gastroscopy, but the correct diagnosis was made at immediate operation, made necessary by gastroscopic perforation of the stomach. It proved to be an ulcer-cancer

In addition to history taking and physical examination, the methods used in investigating these ulcers have been the barium meal, fractional test meal, and gastroscopy. During treatment further evidence of innocence is provided by gain in weight and radiological and gastroscopic evidence of healing.

It is most important not to label a giant innocent ulcer as malignant. The great majority of these ulcers are innocent but require careful treatment. To regard a large ulcer like that of Case 2 (Fig. 4) as malignant and therefore beyond the reach of surgery is to expose the patient to the very serious risk of haemorrhage and death from an innocent condition. Fig. 4



Case 2 Case 60 Case 65

FIG. 4.—Three giant innocent ulcers with radiological appearances that suggested malignancy.

shows the films of Cases 2, 60, and 65 in which the radiological appearances suggested malignancy but histological examination of the ulcers excised at operation showed them to be innocent.

Treatment

Fifty-two patients were treated by medical measures for varying lengths of time. All were treated in hospital, as it is thought that in-patient treatment at the start and for as long as the patient is content is the most satisfactory method of medical treatment. These are ill patients, in considerable risk of haemorrhage from their ulcers, and it is important that healing should start as soon as possible. The rate at which healing is occurring is observed by studying comparable radiological views of the ulcer, and a decision must be made whether elective surgery or medical treatment is indicated. However, it may not be possible to make this decision until the patient has been in hospital for about six weeks.

Elective Surgery

Elective surgery was regarded as the correct primary treatment for 13 patients—in two because of gastric retention, in one because of uncertainty about the character of the ulcer, and in 10 because of the length of gastric history. A preliminary course of medical treatment was given to all these patients. In addition to improving their nutrition, it is very desirable in certain cases with high ulcers to secure some healing of the ulcer before resorting to surgery, so that as much of the stomach as possible can be preserved.

A further 21 patients were treated by elective surgery because their ulcers either failed to heal under medical treatment or recurred after healing.

A Billroth I partial gastrectomy was the operation of choice and elective surgery was carried out on 34 patients without loss.

Medical Treatment

The principal item in the medical treatment of these patients is bed rest except for toilet purposes. A light nourishing diet with extra milk is given and suitable sedation and antacids are prescribed as required. A special effort is made to maintain the patient's morale and to secure his understanding and co-operation in the tedious treatment.

Differing opinions have been expressed about the value of medical treatment of these giant ulcers. Jennings and Richardson (1954) think it well worth while, but that dieting and rest are rarely necessary. Marshak *et al.* (1953) consider that medical measures have nothing to offer. Avery Jones (1957) has said that "a large gastric ulcer with a short history may heal completely and a medical trial is worth while, but the prognosis is poor if there are other associated illnesses."

Thirty-nine patients were treated medically with a view to getting the ulcer healed, but three ceased attending before healing occurred. The result of the primary medical treatment of the remaining 36 patients was: ulcers healed, 21 ; and ulcers failed to heal, 15.

Ulcers that Failed to Heal (15).—The ulcers of 15 patients (7 male, 8 female) failed to heal under prolonged medical treatment. One patient died of carcinoma of the larynx. Of the remaining 14, 13 were treated by elective gastrectomy and one by emergency gastrectomy for haemorrhage, which caused his readmission to hospital.

Ulcers that Healed (21).—The ulcers of 21 patients (15 male, 6 female) healed under medical treatment. It is desirable to have final gastroscopic as well as radiological evidence of healing, because an ulcer can be so nearly healed that there is no longer a crater to fill with barium. However, the breach of mucosa can be seen with the gastroscope. At this stage the patient is symptom-free, so that the absence of symptoms is not proof of healing. The average time taken for these ulcers to heal was six and a half months. Five healed in under two months and eight in under three months. In this group that healed were two ulcers of 5 cm. in diameter and one of 6 cm. The latter required three and a half months' in-patient treatment and two and a half months' out-patient treatment to obtain radiological healing. Three months later symptoms recurred and a Billroth I gastrectomy was performed. The two ulcers of 5 cm. diameter also recurred.

Recurrences (14).—In 14 patients (12 male, 2 female) recurrent ulceration took place after healing of the original giant ulcer. In two cases the recurrence was associated with the patient's fatal illness from another cause ; in a third case with the death of the patient's wife ; in a fourth with the wife's illness ; in a fifth with domestic disharmony ; and in a sixth with whisky drinking. Thus in 6 out of the 14 cases there is a possible reason for the recurrence. Nine out of the 14 patients had their recurrence within six months of the date of healing and 12 within a year. This suggests a more hopeful outlook for those whose ulcers remain healed for over a year. In two patients recurrent ulcers have healed again and remained healed for about four years in each case. Of the remaining 12, eight have had partial gastrectomy, two have refused surgery, and two, as already mentioned, have died.

Ulcers that have Remained Healed (8).—The ulcers of eight patients (5 male, and 3 female) have remained healed for periods varying from two to five years. All of them have had barium meals within the past year, followed in some cases by gastroscopy. A ninth patient is placed in the "probably healed" category only because her last negative barium-meal examination was two years ago. Her giant ulcer healed two and a half years ago and she remains symptom-free.

FIG. 5.—Case 51. One of the eight successes of medical treatment.

In Fig. 5 is seen the giant ulcer of one of the eight patients in this group with long-term healing (Case 51). His ulcer, measuring 4 cm. in diameter, was gastroscopically healed after 15 weeks' treatment. It has remained healed for over two years, and he is the only patient with chronic bronchitis in the group with long-term healing.

Discussion

Table IV summarizes the results of treatment of the 73 patients in this series. It has been shown that these

TABLE IV.—*Summary of Results of Treatment of 73 Patients with Giant Gastric Ulcers*

Emergency surgery	22 (8 deaths)
Elective	34 (No deaths
Ulcers remain healed	8
Ulcer probably remains healed	1
Recurrent ulcers	2
Defaulted	3
Died (other diseases)	3

giant ulcers can be healed, as, using strict criteria of healing, 8 (22%) out of 36 treated medically have remained healed for two years and upwards. These eight patients are our successes. Is there any way in which they could have been picked out of the original 36 and so avoided much time-consuming and unsuccessful medical treatment for the other 28 ? With this aim in view various factors have been analysed.

Sex.—Of 22 men and 14 women who were treated medically, five men and three women are in the group that remains healed. The sexes are thus represented in almost the same proportions in the two groups. Among the 14 patients whose ulcers recurred there are only two women and the recurrence of one was during her terminal illness. It may be that when a giant ulcer heals in a woman it is more likely to remain healed than in a man.

Length of History.—The group of eight who have remained healed are equally divided between those with a gastric history of up to one year and those with a history of over one year.

Size of Ulcer.—The average size of the ulcer is smallest (3.7 cm.) in the group that has remained healed. Of six ulcers treated medically whose diameters were 5 cm. or more, only three healed and they all recurred.

Duodenal Ulcer.—Four patients in the group treated medically had evidence of previous duodenal ulcers but in none of these has the gastric ulcer remained healed.

Effect of Treatment on Weight.—Avery Jones (1957) has said that patients who put on weight usually do well, but the figures for this series do not support that conclusion. Out of the group of eight, whose ulcers have remained healed, five (62%) put on weight (7–37 lb.; 3.2–16.8 kg.) during treatment. Information about weight increase is available for only 12 of the 15 whose ulcers failed to heal. Eight (66%) of these 12 patients put on weight (8–21 lb.; 3.6–9.5 kg.). Thus the proportions that put on weight in each group are similar.

A Possible Plan of Treatment

An effort has been made to find out what factors, if considered early in treatment, can enable one to select those whose ulcers are likely to heal and remain healed. It must be confessed that no obvious method of selection has been discovered, but the following points have been suggested by the investigation.

Surgical treatment is indicated for ulcers of 5 cm. diameter and upwards. If the ulcer heals, presumably the scar is a permanent site of lessened mucosal resistance (Illingworth, 1956). Chronic bronchitis seems to be another factor in favour of surgical treatment. During the initial period of in-patient treatment the rate of healing can be assessed and a decision made on whether treatment should be medical or surgical. If healing is likely to occur reasonably quickly, by which is meant in 8 to 10 weeks, and there are no factors apparent that are likely to cause a recurrence, then healing of the ulcer should be sought. Unfortunately in some patients the initial rate of healing is quite fast, only to slow down and perhaps halt altogether. Finally, there is the attitude of the patient which is all important. Is he able and willing to undergo prolonged bed rest, preferably in hospital ? This point will greatly influence the treatment given.

A high proportion of these patients will require surgical treatment either by emergency surgery for haemorrhage or by elective surgery after a preliminary period of medical treatment. In this series, which may be described as having been very conservatively treated, 77% of the patients have already had surgical treatment. If the series is looked at with hind sight it may be said that too much time has been spent on treating cases medically, but this has been a largely uncharted road and it has been necessary to explore the possibilities of medical treatment.

Summary

A series of 73 giant innocent gastric ulcers, measuring at least 3 cm. in diameter, is reported.

The age incidence of the patients, the size and situation of the ulcers, the length of gastric history, and factors of possible aetiological significance are given.

Pain was the principal symptom in 41 (56%) patients and haemorrhage in 25 (34%).

Emergency surgery was required for haemorrhage in 21 patients, of whom seven died. There were five perforations with one death.

The distinction between the giant innocent ulcer of the lesser curve and the malignant one is discussed. Two cases of giant malignant ulcer of the lesser curve are described.

Eight ulcers out of 36 treated medically have remained healed for two to five years.

Thirty-four patients were treated by elective partial gastrectomy without loss.

A method of selection for medical or surgical treatment is described.

It will be apparent how much the diagnosis and treatment of these patients has depended on the careful radiology which was carried out by Drs. G. Osborne, F. L. Rayner, and W. Stachurko. I am also grateful to Mr. W. W. Davey for much help in the preparation of this paper.

REFERENCES

Illingworth, C. F. W. (1953). *Peptic Ulcer*, p. 74. Livingstone, Edinburgh and London.
—— (1956). *J. roy. Coll. Surg. Edinb.*, **2**, 14.
Jennings, D., and Richardson, J. E. (1954). *Lancet*, **2**, 343.
Jones, F. A. (1957). *Brit. med. J.*, **1**, 786.
Lumsden, K. (1950). *Gastroenterologia (Basel)*, **76**, 89.
Marshak, R. H., Yarnis, H., and Friedman, A. I. (1953). *Gastroenterology*, **24**, 339.
Reid, R. T. W. (1954). *Med. J. Aust.*, **2**, 254.
Shanks, S. C., and Kerley, P (1958). *A Text-Book of X-ray Diagnosis*, 3rd ed., **3**, 160. Lewis, London.
Tanner, N. C. (1954). *Postgrad. med. J.*, **30**, 448.

In 1957 in England and Wales 9,273 sets of twins were born, 95 sets of triplets, and 3 sets of quadruplets. Of the quads, one set comprised 4 liveborn females, one set 2 liveborn males and 2 liveborn females, and one set 2 liveborn females and 2 stillborn males. The birth rate of 16.1 per thousand population was the highest since 1949 (though it was exceeded in 1958, when it was 16.4), and the number of divorces (23,785) was the lowest since 1945. In addition 462 marriages were annulled, also the lowest total since the war.—*Registrar-General's Statistical Review of England and Wales*, 1957, Part II, Tables, Civil. H.M.S.O., 11s. 6d. net.

PLACE OF METHYL PHENIDATE HYDROCHLORIDE IN PSYCHIATRIC PRACTICE

BY

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There is a growing Continental and American literature about the interesting new cerebral-stimulating drug, the hydrochloride of phenyl-(α-piperidyl)-acetic acid methyl ester (methyl phenidate hydrochloride, "ritalin"), but, apart from a preliminary communication on its effects on monkeys by Cole and Glees (1956), a passing reference by Cooper (1956), and a report of negative findings in the treatment of chronic schizophrenics by Salisbury and Hare (1957), there is no mention of it in the British medical press. As it appears to be a drug having a definite place in psychiatric practice, I am describing my preliminary experience with it during the last 18 months.

Meier *et al.* (1954) demonstrated that in experimental animals methyl phenidate has a psychomotor-stimulating effect differing from that of amphetamine and caffeine—its classification, according to them, being somewhere between these two drugs. Workers with human volunteers (Heiss *et al.*, 1956; Drassdo and Schmidt, 1954a, 1954b) showed that methyl phenidate had a stimulating action, and the latter investigations, as well as those of Rizzi (1954) and Bellucci (1955), demonstrated that it antagonized and shortened the action of barbiturates.

Clinically, Ferguson (1955), Stier (1955), Geller (1955), Zahn (1955), Jacobson (1956), Natenshon (1956), Davidoff *et al.* (1957), and Pennington (1957), have shown methyl phenidate to be of value in treating patients suffering from depression.

Although methyl phenidate alleviates the depressive side-effects of reserpine used in the treatment of schizophrenic patients (see below) it does not appear to benefit schizophrenic subjects *per se*, if anything making their symptoms more active (Stier, 1955; Carey *et al.*, 1956; Clark *et al.*, 1956).

Ferguson and Funderburk (1956) obtained an improvement in the behaviour of senile patients. Daly and Yoss (1956) found methyl phenidate of value in treating narcolepsy.

Plummer *et al.* (1956), experimenting with dogs, produced evidence suggesting that methyl phenidate has a specific antagonistic action to reserpine within the central nervous system. Clinically, Ferguson (1955), Ferguson *et al.* (1956), Jacobson (1956), Carter (1956), Mielke (1956), and Madi and Kovitz (1956) have shown that methyl phenidate is of value in the treatment of the side-effects of reserpine, particularly depression.

Thus methyl phenidate has been shown to be of value in the treatment of psychiatric symptoms and in the treatment of the side-effects of reserpine therapy. In both cases the most dramatic effects were on depressive symptoms.

As in the review of the literature, my clinical material naturally falls into two parts: (1) the treatment of psychiatric symptoms and (2) the treatment of the undesirable side-effects of reserpine.

Treatment of Psychiatric Symptoms

Oral Methyl Phenidate (see Table I)

Over the last 18 months, 26 patients suffering from minor psychiatric disorders were treated at the Royal Hampshire County Hospital, Winchester, and Aldershot General Hospital as out-patients with methyl phenidate by mouth in doses up to 20 mg. twice a day. At first, selection was based on the presence of depression, but, later, patients with anxiety were added. The other symptoms listed in Table I were accompanied by depression or anxiety. One of the depressed patients also had a course of E.C.T., but she refused this treatment until her agitation and depression had been relieved by methyl phenidate. The patient with homosexual preoccupation had a marked reduction in his masturbation with homosexual fantasy.

TABLE I.—*Symptomatic Effect of Oral Methyl Phenidate in a Group of 26 Out-patients*

	Total	Completely Relieved	Greatly Improved	Slightly Improved	No Change	Slightly Worse	Worse	Much Worse
Depression	21	10	5	2	3	—	1	—
Endogenous	4	4	—	—	—	—	—	—
Mixed	4	1	—	1	2	—	—	—
Atypical	8	3	5	—	—	—	—	—
Reactive	3	1	—	1	—	—	1	—
Post-influenzal	1	1	—	—	—	—	—	—
Post-concussional	1	—	—	—	1	—	—	—
Anxiety	7	—	—	1	3	1	—	2
Obsessional symptoms	4	—	—	—	4	—	—	—
Hysterical symptoms	6	—	—	1	3	—	1	1
Schizophrenic features	3	—	—	—	1	1	—	1
Ejaculatio-praecox	1	—	—	—	1	—	—	—
Homosexual preoccupation	1	—	1	—	—	—	—	—

Superficial psychotherapy was given to the patients in this section as required.

Intravenous Methyl Phenidate

Intravenous methyl phenidate was not used in the treatment of severe endogenous depression, as modified electric convulsion therapy was the standard treatment in such cases. Such treatment is now regarded as justifiable. Intravenous methyl phenidate was used in three atypical cases.

Case A.—A youth aged 17 suffering from katatonic stupor, possibly related to a head injury, which could temporarily be relieved dramatically by intravenous amylobarbitone sodium, showed no response to 20 mg. of methyl phenidate intravenously, so far as his state of consciousness went.

Case B.—A spinster aged 53 with a mixed depressive state, who had had a leucotomy and was becoming dependent on dextroamphetamine, became cheerful and talkative and much less inhibited about her past after 20 mg. of methyl phenidate intravenously. She enjoyed the experience and was temporarily kept in a less depressed state with methyl phenidate by mouth up to 40 mg. a day.

Case C.—A man aged 46, suffering from a mixed depressive and neurasthenic condition, became more talkative and disinhibited about his past after 20 mg. of methyl phenidate intravenously. He said he was more energetic for the rest of the day, but relapsed to his previous condition next day. Methyl phenidate by mouth improved his mood and energy.

Patients B and C showed a significant rise in pulse and blood pressure.

Treatment of Undesirable Side-effects of Reserpine

The patients described in this section were all in-patients at Park Prewett or Pinewood Hospitals, Basingstoke; all had a clear-cut diagnosis of schizophrenia, and the majority had a history of the present attack lasting for less than two years. Their treatment consisted of a course of reserpine beginning with a 5-mg. intramuscular injection on the first evening, followed by 1 mg. three times a day by mouth and 10 mg. at night for about 12 weeks and then by a maintenance dose of 1 mg. three times a day by mouth for a further period of weeks. The above doses had occasionally to be reduced because of side-effects, particularly a slowing of the pulse below 50 a minute and a fall in the diastolic blood pressure to below 50 mm. of mercury. These patients are part of a further therapeutic study.

The chief side-effects observed were restlessness, depression, and abnormal fatigability, often combined with an extrapyramidal type of rigidity with a tremor often indistinguishable from a slow shiver. Restlessness, together with stiffness and fatigability produced a particularly unpleasant state of affairs, the patient feeling that he wanted to be active but at the same time being overcome by inertia. Mask-like facies, puffiness of the face, drooling from the mouth, nasal congestion, difficulty in breathing, polydipsia, and polyuria were also seen. The tremor was more pronounced if the patients were cold. Seven patients showing some of these signs or symptoms were given oral methyl phenidate alone, and 11 were given the drug intravenously as well as orally.

Oral Methyl Phenidate (see Table II)

Seven cases with minor side-effects were treated with oral methyl phenidate. Three had signs of extrapyramidal dysfunction with restless depression, three had restless depression alone, and one had restlessness alone. The extrapyramidal signs cleared up, as did the restlessness. Two of the patients, both of whom had an initial depressive element, remained depressed and one had to have E.C.T. after completing his reserpine course.

TABLE II.—*Effect of Oral Methyl Phenidate on the Side-effects of Reserpine in Seven Patients*

	Total	Completely Relieved	Persistence of Depression Present Prior to Reserpine
Extrapyramidal dysfunction	3	3	—
Restless depression ..	6	4	2
Restlessness without depression	1	1	—

Intravenous Methyl Phenidate (see Table III)

Three patients were given 10 mg. of methyl phenidate intravenously and eight were given 20 mg.

TABLE III.—*Effect of Intravenous Methyl Phenidate on Side-effects of Reserpine in 11 Patients*

	Total	Completely Relieved
Depression with or without restlessness ..	9	9
Extrapyramidal symptoms	10	10
Restlessness without depression	2	2
Difficult breathing and nasal congestion ..	2	2

The results were as follows.

Case 1.—A spinster aged 27 with hebephrenia became depressed after three days on reserpine. She "felt terrible" and had a coarse shivering tremor. Within a minute of the intravenous injection of 10 mg. of methyl phenidate she relaxed, ceased to shiver, and said she was no longer "out of this world" and felt much better. She became more psychotic in that she was very sexually preoccupied and uninhibited. She completed her course of reserpine with no further unpleasant side-effects on oral methyl phenidate.

Case 2.—A spinster aged 40 with paranoid schizophrenia felt "horrible" after 10 days on reserpine. She was restless, agitated, depressed, and did not know how to occupy herself. She had Parkinsonian facies, with drooling and rigidity and tremor of arms. On 30 mg. of methyl phenidate daily by mouth she felt less "jittery" and restless and less depressed. The signs of extrapyramidal dysfunction were still present but less marked. When given 10 mg. of methyl phenidate intravenously, she gave a deep sigh and said she felt much more comfortable. She became much more talkative and productive in a psychotic manner. The improvement in her mood and muscle tone was maintained to the end of her treatment with oral methyl phenidate.

Case 3.—One month after beginning a course of reserpine a spinster aged 22 with hebephrenia was "jittery," restless, and depressed, and felt stiff. She showed Parkinsonian facies and cogwheel rigidity of the limbs. She was retarded. After 10 mg. of methyl phenidate intravenously all stiffness and retardation went. She felt better and happier. The extrapyramidal signs disappeared. Her B.P. rose in 10 minutes from 100/60 to 160/100. She continued without side-effects to the end of her course on oral methyl phenidate.

Case 4.—A man aged 34 with hebephrenic and paranoid schizophrenia felt restless, depressed, and stiff, and showed marked cogwheel rigidity of the arm 13 days after beginning reserpine treatment. He also had a coarse shivering-like tremor of the arms. After 20 mg. of methyl phenidate intravenously he felt confident and cheerful. He was no longer restless. The tremor disappeared, and the tone of his arms returned to normal. His talk, from being rather retarded, became very productive, with much flight of ideas and psychotic content. His B.P. rose from 110/68 to a maximum of 170/100 after 20 minutes. His pulse rose from 70 to 100 a minute. He said he felt more relaxed and enjoyed the experience. He completed his course of reserpine on oral methyl phenidate without a recurrence of the side-effects.

Case 5.—A girl aged 19 with hebephrenia felt miserable and cried 25 days after beginning reserpine. She was tense and restless, had puffiness of the face and looked pale. She said breathing was difficult. After 20 mg. of methyl phenidate intravenously she said her breathing was easier and she felt better and more wide awake. She also said she felt warm, and this was accompanied by an improvement in her colour. She no longer felt restless. In spite of oral methyl phenidate the restlessness and unpleasant effect recurred, resulting in a reduction in reserpine.

Case 6.—Two days after beginning reserpine therapy a married woman aged 32 with paranoid schizophrenia showed a marked tremor like a coarse shiver and said she felt a very unpleasant restless sensation and that her limbs seemed as if they were swelling. The tremor and unpleasant sensation disappeared after 20 mg. of methyl phenidate intravenously. She became very talkative and unconcerned, although she produced more paranoid material, which would have distressed her previously. Her B.P. rose from 120/70 to 170/110 in 15 minutes. She showed little further side-effects until about eight weeks later, when she became very depressed and suicidal. On 30 mg. of methyl phenidate daily by mouth her mood improved again and she completed the course without further side-effects.

Case 7.—A spinster aged 37 with paraphrenia felt "edgy," restless, and lethargic 14 days after beginning a course of reserpine. She showed a mild tremor but no rigidity. After

20 mg. of methyl phenidate intravenously the tremor ceased and she became very cheerful and discussed her delusions very freely. She complained of palpitation and required reassurance about this. Her B.P. rose from 140/72 to 164/90 in 30 minutes and her pulse from 56 to 100. She went no further with her treatment, as she was uncooperative.

Case 8.—A man aged 24 with hebephrenia was restless and depressed and showed a marked tremor 13 days after starting a course of reserpine. These complaints responded in part to oral methyl phenidate. Three and a half months later, while still on oral reserpine, he was given 20 mg. of methyl phenidate intravenously in an attempt to clear up the continuing restless depression. His pulse rose from 60 to 108, and his B.P. from 120/68 to 200/80. He became anxious and required reassurance that he was not going to die. The restlessness and depression cleared up and did not recur on continuance of the oral methyl phenidate.

Case 9.—Fourteen days after starting a reserpine course a man aged 34 with paranoid schizophrenia and a depressive element was so depressed that he wished he were dead. He was restless. He showed a tremor and cogwheel rigidity of the limbs. After 20 mg. of methyl phenidate intravenously he became subjectively and objectively elated. He became very talkative, particularly about his delusions of persecution, but appeared carefree about them. The tremor and cogwheel rigidity disappeared. His B.P. rose from 110/78 to 150/100 in 20 minutes. There was no recurrence of the extrapyramidal dysfunction on oral methyl phenidate but the depression recurred and necessitated a course of E.C.T.

Case 10.—A man aged 27 with bizarre hypochondriasis, schizophrenic in origin, was restless, listless, and depressed eight days after commencing a course of reserpine. He showed extrapyramidal rigidity and tremor of the limbs. After 20 mg. of methyl phenidate intravenously he said he felt exceptionally comfortable and at ease. He talked freely, but his hypochondriacal ideas were more pronounced and bizarre, although he was less distressed by them. He was no longer restless or listless. With the exception of the listlessness, which returned, he continued his reserpine course without side-effects while on oral methyl phenidate.

Case 11.—Nineteen days after beginning a course of reserpine a youth of 18 with acute hebephrenia showed an expressionless and puffy face, nasal congestion, lead-pipe rigidity of limbs, and a Parkinsonian gait. He was very retarded. After 20 mg. of methyl phenidate intravenously the extrapyramidal signs, nasal congestion, and retardation disappeared. He became very talkative and produced much psychotic material. He became very agitated and feared he was going to die. His pulse rose from 80 to 122 and his B.P. from 130/70 to 180/110. He remains more alert and without signs of extrapyramidal dysfunction, although his reserpine course has not yet been completed.

Depression with or without restlessness was relieved in the nine patients showing this symptom; Parkinson-like symptoms were relieved in the 10 patients having these symptoms; restlessness without depression was relieved in the two patients having this symptom; and difficult breathing with nasal congestion was relieved in the two patients who showed this. There was a significant rise in blood pressure and pulse in the seven patients in whom they were recorded. In eight patients the psychotic behaviour and delusions became more marked, although the patients showed less concern over such symptoms.

Summary and Conclusions

Evidence from the literature suggests that methyl phenidate is a useful drug in the treatment of depression and of the side-effects of reserpine therapy, particularly depression. It would appear to increase the behaviour disturbance and abnormal thought processes of schizophrenic patients.

In a group of 26 out-patients treated with methyl phenidate by mouth there was a marked overall improvement in the depression. This was least marked when there was a considerable reactive element. Anxiety on the whole was made worse, as were schizophrenic features and hysterical symptoms. Obsessional symptoms were not affected.

In one patient with katatonic stupor, no effect of 20 mg. methyl phenidate given intravenously was noticed in the state of consciousness.

In two other non-schizophrenic patients, intravenous methyl phenidate relieved depression and made the patients more talkative and less inhibited.

In 18 patients showing undesirable side-effects of reserpine therapy, dramatic improvement was shown by 10 out of the 11 receiving intravenous methyl phenidate. Anxiety, behaviour disturbance, and schizophrenic thought disorder were increased. In the one case that did not respond well the cause was an exacerbation of anxiety, probably due to an overdose for this particular patient.

Methyl phenidate hydrochloride ("ritalin") has a place in the treatment of depression but none in the treatment of hysterical or obsessional symptoms, and is contraindicated in the presence of anxiety symptoms. It also has a place in the treatment of the side-effects of reserpine. With the exception of this last-mentioned effect it has no place in the treatment of schizophrenia.

Although no attempt has been made at statistical control of the results, their consistency and the dramatic response to intravenous therapy strongly supports their validity.

I thank Dr. I. Atkin, physician-superintendent, and my other colleagues at Park Prewett Hospital for their co-operation and interest, also Ciba Ltd., who supplied the ritalin and reserpine.

REFERENCES

Bellucci, G. (1955). *Minerva anest. (Torino)*, **21**, 125.
Carey, B., Weber, M., and Smith, J. A. (1956). *Amer. J. Psychiat.*, **113**, 546.
Carter, C. H. (1956). *Psychiat. Res. Rep. Amer. psychiat. Ass.*, No 4, p. 44.
Clark, L. D., Ellsworth, R. B., Barrett, W. W., Thurman, A. C., and Holland, W. (1956). *Dis. nerv. Syst.*, **17**, 317.
Cole, J., and Glees, P. (1956). *Lancet*, **1**, 338.
Cooper, P. (1956). *Brit. overseas Pharm.*, **109**, 221.
Daly, D. D., and Yoss, R. E. (1956). *Proc. Mayo Clin.*, **31**, 620.
Davidoff, E., Best, J. L., and McPheeters, H. L. (1957). *N.Y. St. J. Med.*, **57**, 1753.
Drassdo, A., and Schmidt, M. (1954a). *Med. Mschr.*, **8**, 306.
—— —— (1954b). Ibid., **8**, 393.
Ferguson, J. T. (1955). *Ann. N.Y. Acad. Sci.*, **61**, 101.
—— and Funderburk, W. H. (1956). *J. Amer. med. Ass.*, **160**, 259.
—— Linn, F. V. Z., Sheets, J. A., and Nickels, M. M. (1956). Ibid., **162**, 1303.
Geller, W. (1955). *Medizinische*, **1**, 606.
Heiss, R., Becker, H., Hiltmann, H., and Honsberg, I. (1956). Ibid., **1**, 260.
Jacobson, A. (1956). *Med. Ann. D.C.*, **25**, 491.
Jochheim, K. A. (1955). *Med. Klin.*, **50**, 864.
Madi, L. M., and Kovitz, B. (1956). *Antibiot. Med.*, **3**, 309.
Meier, R., Gross, F., and Tripod, J. (1954). *Klin. Wschr.*, **32**, 445.
Mielke, F. A. (1956) *Schweiz. med. Wschr.*, **86**, 162.
Natenshon, A. L. (1956). *Dis. nerv. Syst.*, **17**, 392.
Pennington, V. M. (1957). *J. Amer. Geriat. Soc.*, **5**, 421.
Plummer, A. J., Maxwell, R. A., Earl, A. E., and Rutledge, R. (1956). *Fed. Proc.*, **15**, 468.
Rizzi, R. (1954). *Arch. Osp. Mare*, **6**, 23.
Salisbury, B. J., and Hare, E. H. (1957). *J. ment. Sci.*, **103**, 830.
Stier, C. (1955). *Ther. d. Gegenw.*, **94**, 92.
Zahn, L. (1955). *Berl. Gesundh.-Bl.*, **6**, 419.

EFFECT OF INTRA-ARTERIALLY ADMINISTERED NICOTINE ON THE BLOOD FLOW IN THE HAND

BY

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It is a well-known fact that smoking produces vasoconstriction in the human skin. Intravenous injections of nicotine in doses corresponding to those assumed to be absorbed after smoking a single cigarette cause a vasoconstriction comparable to that caused by smoking a cigarette (Maddock and Coller, 1933). The vasoconstriction following smoking has therefore been attributed to the nicotine content of the smoke. Smoking did not cause vasoconstriction in sympathectomized limbs or in limbs after blocking the sympathetic nerves (Maddock and Coller, 1933; Roth *et al.*, 1944). Consequently the action of nicotine was thought to be mediated via the sympathetic nerves. So far there has been no indication of a direct peripheral vascular action of nicotine in man. In animals, however, it has repeatedly been shown (for references see Burn and Rand, 1958) that nicotine can excite the smooth muscle of blood vessels when applied direct to the vessels in an organ bath or when given intra-arterially. This effect could be evoked consistently on frog and rabbit vessels but not regularly in the dog.

Methods

Thirteen experiments were made on 11 healthy subjects (seven males and four females).

Throughout the experiment the subject was lying on a couch in a silent room. The room temperature was kept relatively constant during each experiment, but varied between 21 and 24° C. in the different experiments. All drugs were injected through a "polythene" tube introduced into the left brachial artery at the elbow level as described by Bernéus *et al.* (1954). Saline solution or nicotine bitartrate dissolved in saline solution (*p*H about 7) was given in a single injection or with an infusion apparatus at a rate of 1.67 ml./min. Injections of nicotine, hexamethonium bromide, dihydroergotamine, pentolinium tartrate, or dibenamine hydrochloride were given in a volume of 1 ml. of saline solution. The blood flow in the left hand (catheter in left arm), and in a few experiments in the right hand as well, was measured with a venous occlusion plethysmograph. The blood flow was estimated intermittently. Each estimation consisted of five to eight readings taken during one to two minutes. The temperature of the water in the plethysmograph was 32° C.

Results

The intra-arterial injection (Fig. 1) or infusion of nicotine was found to cause vasoconstriction in the hand of the injected limb. The response ensued within a few seconds after the administration and could be repeated several times. The response could be graded by varying the dose given. After a single dose the vasoconstriction lasted only for a short time. No effect was discernible in the contralateral hand.

The infusion of nicotine at a rate of 16.7 μg./min. caused vasoconstriction in three subjects. With an infusion of 83.5 μg./min. vasoconstriction was noted in four further subjects, while the remaining four did not respond measurably to this dose, whereas a single injection of 100 μg. of nicotine was followed by a reduced blood flow. The injection of a corresponding volume of saline had no such effect. Two of the 11 subjects were heavy smokers (more than the equivalent of 30 cigarettes a day), two were medium smokers (5–15 cigarettes a day), and the rest were non-smokers or occasional smokers (a few cigarettes a month). No correlation was found between smoking habit and sensitivity to the vasoconstrictor effect of nicotine. Thus one of the heavy smokers responded to the infusion of 16.7 μg./min., while the other did not respond to the infusions but to the single injection of 100 μg. Infusions of more than 83.5 μg./min. were not regularly used, since such amounts (167 μg./min. was tried) were found to cause an unpleasant pricking sensation in the arm peripheral to the site of the catheter.

Several of the subjects remarked spontaneously on a chilling sensation in the injected limb. This sensation was experienced only during administration of doses of nicotine which caused vasoconstriction as measured plethysmographically.

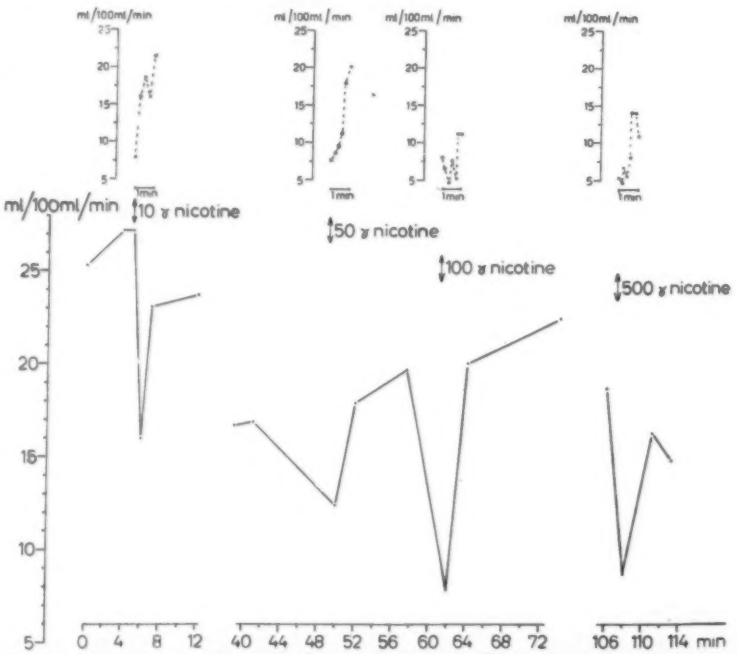

FIG. 1.—In the lower part of the figure is shown the effect of injections of nicotine bitartrate on blood flow in the hand. Nicotine was dissolved in 1 ml. of saline solution. Control injections of 1 ml. of saline solution were given. The upper part shows the readings during one minute following the injections of nicotine, starting 15 seconds after the injection.

Injection of hexamethonium intra-arterially abolished the effect of nicotine as shown in Fig. 2. Pentolinium tartrate (2 mg. intra-arterially) also blocked the vasoconstrictor effect of nicotine. Dihydroergotamine (0.5 mg. intra-arterially) and dibenamine (4 mg. intra-arterially) also prevented the vasoconstriction following infusion of nicotine. However, the injection of dihydroergotamine by itself caused a marked reduction in blood flow. This reduction was greater than that caused by the previous infusion of nicotine, and therefore no firm conclusion can be drawn regarding the blocking effect of this drug. The other three drugs given intra-arterially did not have any marked effect of their own on the blood flow.

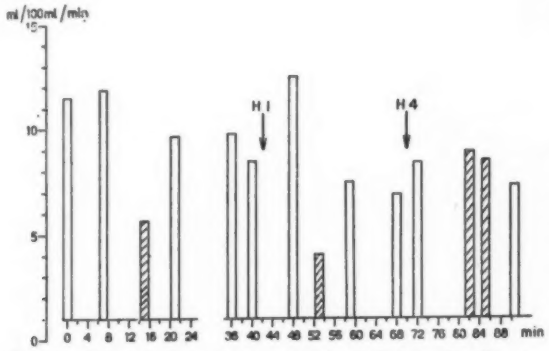

FIG. 2.—Blood flow in the hand during infusion of saline or nicotine bitartrate (83.5 μg./min.). Hatched columns denote nicotine. At the arrows 1 and 4 mg. of hexamethonium bromide were injected.

Discussion

Nicotine has been thought to cause a peripheral vasoconstriction by way of the sympathetic nervous system. The present report shows that nicotine causes an immediate vasoconstriction in the human hand when injected into the brachial artery. This effect is likely to be due to a direct peripheral action of nicotine, especially as vasoconstrictor responses were absent from the contralateral hand.

According to the calculations of Boyle *et al.* (1947), based on the findings of Baumberger (1923), smoking of cigarettes with inhalation will give an absorption of nicotine equivalent to 2 mg. of nicotine bitartrate a minute. The flow in the brachial artery at the site used for infusion may be about one-hundreth of the cardiac output, and hence smoking would correspond to an infusion of some 20 μg./min. in this artery. In the present experiments this was just about the threshold dose for vasoconstriction in certain individuals. Moreover, it is quite possible that during prolonged smoking there may be an accumulation of nicotine in the blood, causing a higher dosage than calculated above. It is therefore likely that in some individuals the amount of nicotine absorbed during smoking is big enough to elicit a direct peripheral effect. These assumptions and calculations are not necessarily contradictory to earlier reports that sympathetic blockade abolishes the vascular effect of smoking, since there are great individual variations in sensitivity, and the early experiments with sympathetic blocking were made in only a few cases.

The mechanism of the peripheral action of nicotine is not known. However, the present observation that sympathicolytic agents prevent the vascular effect of nicotine is compatible with the assumption that nicotine acts by release of sympathicomimetic substances (for references see Burn and Rand, 1958). These substances may be released from the system of chromaffin cells lying close to the small vessels of the human skin (Adams-Ray and Nordenstam, 1956) or they could be released from the store which has been found in the arterial walls (Schmiterlöw, 1948). A release from a chromaffin system would be consistent with the finding that ganglion-blocking agents prevent the effect of nicotine.

Another possible mechanism of the peripheral action of nicotine would be by excitation of a peripheral nervous plexus containing ganglion cells and adrenergic terminals. But so far no such peripheral nervous plexus has been definitely demonstrated (Folkow, 1956).

Summary

Nicotine was found to cause vasoconstriction in the hand when injected into the brachial artery. The threshold doses varied greatly between individuals, but, at least in some, the amount of nicotine assumed to be absorbed during smoking would be enough to cause vasoconstriction via a local mechanism. Sympathicolytics and ganglion-blocking agents abolished the effect of nicotine. This appears consistent with the assumption that nicotine causes a release of sympathicomimetics from the chromaffin system in the human skin, but could also be explained by the existence of a peripheral nervous plexus containing ganglion cells.

The work was carried out at the department of clinical physiology at the University of Göteborg and supported by a grant to that department from Svenska Nationalföreningen mot Tuberkulos och andra folksjukdomar. I am indebted to the head of the department, Professor A. Carlsten, for facilities and to Mrs. Eva Larsson for skilful technical assistance.

REFERENCES

Adams-Ray, J., and Nordenstam, H. (1956). *Lyon chir.*, **52**, 125.
Baumberger, J. P. (1923). *J. Pharmacol. exp. Ther.*, **21**, 35.
Bernéus, B., Carlsten, A., Holmgren, A., and Seldinger, S. I. (1954). *Scand. J. clin. Lab. Invest.*, **6**, 217.
Boyle, M. N., Wégria, R., Cathcart, R. T., Nickerson, J. L., and Levy, R. L. (1947). *Amer. Heart J.*, **34**, 65.
Burn, J. H., and Rand, M. J. (1958). *Brit. med. J.*, **1**, 903.
Folkow, B. (1956). In *The Control of the Circulation of Blood*, Supplemental Volume, edited by R. J. S. McDowall, p. 1. Dawson, London.
Maddock, W. G., and Coller, F. A. (1933). *Ann. Surg.*, **98**, 70.
Roth, G. M., McDonald, J. B., and Sheard, C. (1944). *J. Amer. med. Ass.*, **125**, 761.
Schmiterlöw, C. G. (1948). *Acta physiol. scand.*, **16**, Suppl. 56.

In a sophisticated society the parents to whom a mentally subnormal child is born have a sad and difficult adjustment to make. Several books and pamphlets have appeared in recent years to help them " fashion from their disappointment a hope and a purpose " to give them new strength and understanding. These words are taken from the opening chapter of a handbook recently published for the Australian Council of Organizations for Subnormal Children (*The Subnormal Child at Home*, Macmillan, 5s.). The authors are F. J. Schonell, J. A. Richardson, and T. S. McConnel. They give a clear account, with neat illustrations, of how subnormal children can be helped to develop their faculties and, when possible, become self-supporting. The book would probably be of help to doctors who have to advise the parents of such children ; it would certainly be useful in the hands of intelligent parents confronted with this problem.

Preliminary Communications

"1314" in Pulmonary Tuberculosis

We have been concerned in the early clinical trial of a new substance, alpha-ethyl*iso*nicotinic thioamide (" 1314 "), synthesized by Libermann *et al.* (1956). This compound is not a derivative of isoniazid, but, like isoniazid, a derivative of isonicotinic acid. Its use in tuberculosis is being explored because Rist *et al.* (1958) showed that it was active *in vitro* against isoniazid-resistant tubercle bacilli and that cross-resistance apparently did not occur.

Brouet (1958) treated with 1314 alone 18 patients who had minimal disease and a positive sputum. Organisms resistant to the drug emerged in three patients at the end of three months' treatment. Loss of sensitivity to 1314 was not recorded when it was combined with isoniazid, streptomycin, and other antibiotics, though detailed information is awaited.

In an attempt to delay the development of resistance we combined 1314, 1 g., with tetracycline, 4 g., both in two divided doses daily. Tetracycline was used because it has only very slight antituberculous activity but may delay the emergence of resistance to certain antituberculous drugs (Stewart *et al.*, 1954; Murdoch and Stewart, 1956). We were therefore able to assess the antituberculous activity of 1314 more accurately than if it had been given in combination with a more effective drug.

Seven patients with chronic advanced pulmonary tuberculosis whose bacilli were known to be resistant to streptomycin, *para*-aminosalicylic acid, and isoniazid were treated with the combination of 1314 and tetracycline. The trends of sputum positivity were studied by weekly viable counts. The sputum became negative on culture in one patient after five weeks' treatment, and has remained so during a subsequent 27 weeks' follow-up. This patient had had a positive sputum for at least seven years. A second patient showed a marked decrease in sputum positivity, but occasional positive cultures have been obtained up to 17 weeks; no resistance has yet been demonstrated. An initial reduction in sputum positivity occurred in a further four patients, but there was a subsequent rise in positivity while still on treatment. In all four cases organisms resistant to 1314 were detected after 5, 7, 8, and 18 weeks' treatment. The seventh patient showed a reduction in sputum positivity, but resistant organisms were detected at the third week and the patient died three weeks later.

Drug intolerance in the form of nausea and sometimes vomiting proved troublesome in six out of the seven patients. In several it necessitated reduction of dosage or even temporary cessation of treatment.

CONCLUSION

Our preliminary bacteriological evidence suggests that 1314 is an effective antituberculous drug but that tetracycline will prove relatively ineffective in preventing resistance to it. On present dosage nausea and vomiting are likely to prove troublesome in a number of patients.

We suggest that at this stage it would be inadvisable for physicians to hazard their patients' future by premature use of a potentially powerful drug. The result may be a few weeks' improvement at the expense of permanent drug-resistance. Further studies, now being planned through the Clinical Trials Committee of the British Tuberculosis Association, may establish a better tolerated but effective dose and also indicate drug-combinations which will prevent resistance. A wider use of the drug in patients with bacilli resistant to standard chemotherapy may then be justifiable.

We are grateful to Dr. Noël Rist, of the Pasteur Institute, Paris for much information, and to Messrs. May and Baker Ltd. for supplies of 1314, which is known in France as " 1314 T.H."

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REFERENCES

Brouet, G. (1958). *Bull. int. Un. Tuberc.*, **28**, 216.
Libermann, D., Moyeux, M., Rist, N., and Grumbach, F. (1956). *C.R. Acad. Sci. (Paris)*, **242**, 2409.
Murdoch, J. McC., and Stewart, S. M. (1956). *Brit. J. Tuberc.*, **50**, 85.
Rist, N., Grumbach, F., Libermann, D., Moyeux, M., Cals, S., and Clavel, S. (1958). *Rev. Tuberc. (Paris)*, **22**, 278.
Stewart, S. M., Turnbull, F. W. A., and Crofton, J. W. (1954). *Brit. med. J.*, **2**, 1508.

Medical Memoranda

A Case of Twin Pregnancy in a Double Uterus

The patient, aged 39, presented herself at my antenatal clinic on September 19, 1956, with a history of amenorrhoea since May 23, 1956, and early morning sickness and enlargement of the breasts.

Previous Obstetric History.—1943: Spontaneous delivery of a 4-lb. (1,800-g.) boy of 36 weeks' gestation. Severe blue asphyxia due to the cord being round the neck. He responded to treatment and is alive and well. 1945: Spontaneous delivery of a 5-lb. (2,270-g.) boy of 40 weeks' gestation. Precipitate labour. Alive and well. 1949: Miscarriage at 4½ months. 1954: Miscarriage at 10 weeks.

Menstrual History.—Onset at 11, 5–6/25–26; regular.

On examination she was clinically anaemic. A soft systolic murmur was audible all over the praecordium. There was no cardiac enlargement. Her pulse was 76 a minute, blood pressure 120/80. The urine was normal. The uterus was enlarged to three fingerbreadths above the umbilicus. A distinct groove was felt down the anterior wall of the uterus. Movements had not been felt nor could they be heard. Vaginal examination revealed a roomy pelvis with an outlet of more than four knuckles and an internal conjugate of more than 4½ in. (11.4 cm.). Two cervices were present lying side by side. Her blood was group O, rhesus positive. No antibodies were present. The Wassermann and Price reactions were negative. Her haemoglobin was 59% (8.76 g./100 ml.); R.B.C., 3 millions; M.C.H., 29 $\mu\mu$g.; P.C.V., 28%; M.C.H.C., 31%; M.C.V., 93 cubic microns. A diagnosis of twins in a double uterus and anaemia was made. She was treated with " ferromyn," one tablet three times a day after food, and rest in bed at home. On examination a month later it was obvious that the two foetuses were lying a long way apart; this was confirmed on subsequent *x*-ray examination.

The pregnancy continued normally, and by January 10, 1957 (33 weeks), her haemoglobin was 81%. The two foetuses were presenting by the vertex and two foetal hearts could be heard. On January 21 her blood pressure was 140/90; there was pitting oedema of both ankles but no albuminuria.

She was admitted next day and put to bed on a salt-free diet, phenobarbitone, and restricted fluid intake. By January 25 the blood pressure had risen to 160/100, oedema had increased still further, and albumin had appeared in the urine. In view of this, "puroverine," half a tablet four-hourly, was given, and within 12 hours the blood pressure had fallen to 110/70 and the urine become free from albumin. Oedema was still marked, and this, combined with the distended abdomen, made it very difficult for her to rest.

Labour began at 12.5 a.m. on January 27. A vaginal examination at 4 a.m. showed that the cervix was dilated two to three fingerbreadths and irregular in outline. She was given 100 mg. of pethidine and 50 mg. of promethazine hydrochloride intramuscularly, and she slept until 10 a.m. Her pains became much stronger at this stage and by 11.30 a.m. she was fully dilated. Throughout the first and second stages both uteri contracted simultaneously.

At 12.10 p.m. she was delivered of a male child face to pubes. The child was in a state of blue asphyxia and his hands and feet were oedematous. The asphyxia responded to clearing of the air passages and oxygen. His colour never became normal, however, and two hours after delivery he began to have blue attacks and pass large quantities of a clear fluid from his mouth. A fine catheter could not be passed into his stomach, and a diagnosis of oesophageal atresia was made. The baby died at 7.10 p.m.

After delivery, the right side of the abdomen was seen to be empty and all uterine contractions had ceased. It was not possible to make out the usual signs of placenta separation, but, since there was no bleeding, no action was necessary. An hour after delivery the cord lengthened by 4 in. (10 cm.) and there was a slight loss of blood. A vaginal examination showed that the placenta was lying half in and half out of the cervix. It was gently removed and there was no further bleeding. The placenta was small and almost a solid mass of infarcts.

Examination of the abdomen showed that the remaining foetus was lying obliquely with the vertex presenting, but high over the pelvic basin. The foetal heartbeat was quite normal and regular, and the sounds were of good quality. The blood pressure was 148/78.

In view of this and the small size of the first foetus—5 lb. 14 oz. (2,665 g.)—I decided to await the onset of labour in the hope that the second foetus would grow a little bigger, and that the toxaemia would improve now that an infarcted placenta had been expelled.

Hysterosalpingogram taken in April, 1957, showing two uteri with separate cervices.

Twelve hours after delivery she began a profuse diuresis, and within a week her oedema had gone and a central stream of urine showed no albumin. There was no evidence of lactation. By February 15 her blood pressure was steady at 130/80, her oedema had gone, and the head was beginning to engage in the pelvis. On the right-hand side of the uterus an irregularity could be felt, which was the retracted part of the uterus that had contained the first twin.

At 3 a.m. on February 18 her membranes ruptured and at 6 a.m. labour pains began. By 7.40 a.m. she was fully dilated, and at 7.50 a.m. had a normal delivery of a female child weighing 6 lb. 4 oz. (2,835 g.). Ten minutes later the placenta and membranes were expelled complete. The loss was 4 oz. (114 ml.). This placenta appeared quite normal.

The baby cried well and was a good colour from birth. Examination showed no congenital abnormalities.

The puerperium was normal apart from a mild urinary infection which responded to sulphonamides, and she was discharged fully breast-feeding on March 1. Six weeks later the uterus was well involuted and anteverted. Both cervices were healthy and just admitted the tip of the index finger. A hysterosalpingogram showed that there were two uteri with separate cervices, and that the left one was slightly bigger than the right.

COMMENT

Several points arise from this case that merit discussion. (1) What is the mechanism of the onset of labour, bearing in mind that in this case one uterus went into labour whilst the other did not? (2) What causes the uterine muscle to change from contraction and relaxation to retraction? In this case the right uterus was retracting during the expulsion of the first twin whilst the left uterus was undergoing first-stage contractions. (3) What is the cause of toxaemia? This case suggests that placenta infarcts are the cause rather than the result of the toxaemia. (4) What causes lactation to begin?

A review of the literature shows that the only similar case reported is that by Williams and Cumming (1953), where twins were born alive 56 days apart in a patient with a completely double uterus.

I thank Miss L. I. H. Torrance for her help with this case; the matron and staff of Bexley Maternity Hospital for their co-operation and unremitting care; and Dr. F. M. Collins, of the Ministry of Pensions and National Insurance, who supplied me with references to the literature.

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REFERENCE

Williams, B., and Cummings, G. (1953). *J. Obstet. Gynaec. Brit. Emp.*, **60**, 319.

The 1959 volume of the *Modern Treatment Yearbook* (published for the *Medical Press* by Baillière, Tindall and Cox, Ltd., London; price 30s.) is the twenty-fifth in the series. Sir Cecil Wakeley is the editor, and not unnaturally he sees to it that the surgeon's point of view is given proper prominence. The aim of the book is to provide practical information, and among the subjects chosen for discussion are some of the foremost therapeutic topics of the day—hypertension, intervertebral disk protrusion, treatment of cardiac infarction in the home, chronic bronchitis, mental disorders in old age, painful feet, "the cough that kills," tranquillizers, and the treatment of non-vital teeth. The book includes a special section of illustrations on art paper.

Reviews

AMPHETAMINE PSYCHOSIS

Amphetamine Psychosis. By P. H. Connell, M.D., D.P.M. (Pp. 133; illustrated. 21s.) London: Published for the Institute of Psychiatry by Chapman and Hall, Ltd. 1958.

This is the fifth of the Maudsley Monographs. It constitutes an important addition to the literature on the subject of amphetamine addiction. The author begins by reviewing the literature and providing a short review of most of the cases of mental symptoms accompanying overdosage of amphetamine which have been reported in the English and French languages. He then describes 42 patients who had come under his own observation, and comes to general conclusions. In the second part of the book the biochemical tests available for testing the presence of amphetamine, dexamphetamine, and methylamphetamine in body products are discussed; and the author presents as practical and reliable his own modification of the methyl-orange test of Brodie and Udenfriend.

Dr. Connell believes that psychoses associated with amphetamine usage are much commoner than is usually supposed. The acute psychotic state which results from overdosage closely resembles a paranoid schizophrenia, and is commonly so diagnosed; but it usually clears up within a week. If the illness persists, and biochemical tests show that amphetamine has been eliminated, then another cause must be looked for (for example, a genuine schizophrenia). Amphetamine must be regarded as a true hallucinogen, since a single large dose will cause a psychotic state with hallucinations. The medical profession is given a number of well-meant warnings about how the drug should be used.

The psychotic state produced by amphetamine is of much clinical interest. There are no physical signs of any diagnostic significance. Yet an experienced clinician would probably suspect a toxic psychosis if he bore the possibility in mind. Features in which it tends to differ from a schizophrenic state are the past history of psychopathic traits, the rapidity of onset, the dream-like quality of the experiences, the tendency towards visual hallucination, and the brisk emotional reaction usually in the direction of anxiety. Only the most hyperacute of paranoid schizophrenic states will mimic this syndrome in all its peculiarities.

Dr. Connell does not make use of the word "confusion," but says that in only three cases was there disorientation. It seems probable that, with adequate attention to specific tests, a much larger number of the patients would have shown evidence of some degree of clouding of consciousness. We are not told how many of the patients had a clear and detailed, or a muddled and incomplete, idea of what they had gone through, after the first few days of acute disturbance had passed. It is a matter of much theoretical interest how closely a pseudo-schizophrenic symptomatic psychosis may resemble the true endogenous schizophrenia. It is a pity that the author did not go into this in more detail, merely confining himself to saying that the mental picture may be indistinguishable from acute or chronic paranoid schizophrenia. Nevertheless, he is to be congratulated on a substantial and valuable piece of work.

ELIOT SLATER.

FIRST TEN YEARS OF W.H.O.

The First Ten Years of the World Health Organization. (Pp. 538+vii; illustrated. 25s.) Geneva: World Health Organization. 1958.

The First Ten Years of the World Health Organization, published in Geneva, is in three parts: the first, on the early history of international collaboration; the second, on the establishment of the World Health Organization, from the San Francisco Conference onwards; and the third, on the work of the first 10 years. There are 13 appendices, 6 maps, and 3 charts. The main interest of this book lies in Chapters 11–34, which set out what W.H.O. has done in a number of different fields. This constitutes an impressive record, and it is in itself something of a textbook of international public health. There are chapters on malaria, tuberculosis, venereal diseases and treponematoses, virus diseases, zoonoses, international quarantine, epidemiological and health statistical services, atomic energy in relation to health, environmental sanitation, nutrition, mental health, maternal and child health, health education of the public, and a number of other topics. The volume should be a standard textbook for public-health students. It is a mine of information, although, unfortunately, not always written in a very readable style.

FRASER BROCKINGTON.

BETTER A DISH OF HERBS

Where Love Is: The Fostering of Young Children. By Josephine Balls. With a preface by John Bowlby. (Pp. 224. 16s.) London: Victor Gollancz Ltd. 1958.

There are 85,000 children in England and Wales in the care of local authorities and voluntary societies. In 1952 the Northumberland County Council decided to close its residential nurseries for children under 5 years of age and to find foster-homes for the children. This decision was based on the conclusion that institutional care, however devoted and affectionate, did not provide young children with the love and security which they need. It was generally recognized in the nineteenth century that bad institutions harmed the development of growing children, but it was not until World War II, with its experience of the large-scale evacuation of our children, that it became recognized that a bad home might cause less damage to the young child than a good institution. The alternative solution is the foster-home, and Northumberland, since it closed its nurseries, keeps a register of 50 foster-homes to accommodate its deprived children under 5 years old. Although the children in the nurseries were all, in some way or another, abnormal, homes were found for all of them except three mentally defective children. The success of these placings depended on the skill and experience of the visitor appointed to find the appropriate homes; and this book is a practical account of the difficulties, the successes, and the failures.

The final objective of this work among these displaced children is to rehabilitate their homes against their eventual return. Miss Balls does not lose sight of an even more fundamental task, pursued by many agencies, to prevent children coming into the care of local authorities. Her book is well written with illustrative case histories; and, although the time is not yet for an assessment of final success, it is apparent that enthusiasm and understanding will not permit failure. By 1957 three counties and ten county boroughs had closed their nurseries; some following Northumberland's example

for the same reasons, others on economic grounds, for the average weekly cost of a child in a local-authority home is £12. Dr. John Bowlby contributes a characteristic introduction. No mention is made of James Spence, but it is difficult to believe that his ideas did not have their influence on the Northumberland County Council.

D. V. HUBBLE.

GYNAECOLOGY FOR BEGINNERS

Essentials of Gynecology. By E. Stewart Taylor, M.D. (Pp. 502; illustrated. 84s.) London: Henry Kimpton. 1958.

The author of this American textbook of gynaecology "for students and young practitioners" is to be congratulated on an excellent production which will compare favourably with any of its British counterparts. It is a work of modest proportions, yet manages to contain a good deal of information and covers fully the whole field of gynaecology. The material has been carefully selected, and a well-balanced, well-documented, thoroughly up to date, and fully illustrated account of the subject is presented, in which anatomical, physiological, and pathological considerations are correlated with clinical practice.

The arrangement of subject-matter is on a regional basis and for the most part orthodox, but it is a little unexpected to find details of operative treatment dealt with seriatim in the general text, yet supplemented by two further chapters on hysterectomy at the end of the book. Chapters on preventive gynaecology and paediatric gynaecology—the former including a section on examination of the breasts—may strike the reader as somewhat unusual though welcome inclusions, but it is surprising how rarely he will be conscious of the transatlantic origin of this book.

Special mention might be made of the chapters on carcinoma of the female genitalia and those on the endocrine glands, though it is a little invidious to single out features of special merit when the standard throughout the work is so high. This is a textbook that can be confidently recommended to the British undergraduate or postgraduate student wishing to extend the scope of his reading. Unfortunately, it is rather expensive.

MOSTYN P. EMBREY.

FROM FEAR TO UNDERSTANDING

Bridging the Gap from Fear to Understanding in Mental Illness. Edited by R. F. Tredgold, M.D., D.P.M. (Pp. 270; 30s.) London: Christopher Johnson. 1958.

It is explained in the publisher's note that this book "is an attempt to bridge the gap between the old attitude of fear, and a new attitude of understanding towards the mentally ill; and also the gaps between members of the psychiatric services and some of the more embittered and critical patients." The book consists of a series of essays, written by different authorities for what would seem to be quite different audiences. As might be expected, valuable papers are contributed by Dr. J. A. Scott on the work of the mental welfare officers, and of the part played by local authorities in after-care and rehabilitation. Other noteworthy contributions are Dr. J. A. R. Bickford's paper on "The Psychiatrist's Opportunity," and "Rehabilitation and Discharge" by Dr. David Rice. Some of the other contributions do not, however, reach the same high standard.

DESMOND CURRAN.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Schalleitungsschwerhörigkeiten. Ihre Ursachen und Entstehung: Otosklerose. By Professor Dr. E. Müller. (Pp. 89+x: illustrated. DM. 18.) Stuttgart: Georg Thieme Verlag. 1959.

Psychiatry in Medical Practice. By W. Lindesay Neustatter, M.D., B.Sc.(Psy.), M.R.C.P. (Pp. 311+viii. 42s.) London: Staples Press. 1958.

An Irish Doctor's Memories. By Patrick Heffernan, M.D. (Pp. 116; illustrated. 10s. 6d.) Dublin: Clonmore and Reynolds Ltd. London: Burns, Oates and Washbourne Ltd. 1958.

Svenska Läkaresällskapet 150 Ar; dess Tillkomst och Utveckling. En Aterblick. By Hilding Bergstrand. (Pp. 562: illustrated. 50 Sw. Kr.) Stockholm: Svenska Läkaresällskapet. 1958.

Live at Peace with Your Nerves. By Dr. Walter C. Alvarez. (Pp. 267. 21s.) Kingswood, Surrey: The World's Work (1913) Ltd. 1959.

Studies on Fertility. Including papers read at the Conference of the Society for the Study of Fertility, London, 1958. Being Volume X of the Proceedings of the Society. Edited by R. G. Harrison, M.A., D.M. (Pp. 176+x; illustrated. 25s.) Oxford: Blackwell Scientific Publications. 1958.

Neurological and Psychological Deficits of Asphyxia Neonatorum. With Consideration of Use of Primates for Experimental Investigations. By twenty-eight contributors. Edited by William F. Windle, Ph.D., Sc.D. (Pp. 386+xiv; illustrated. 60s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Topométrie Cranio-encéphalique chez l'Homme. Cranio-cerebral Topometry in Man. [Text in French and English.] By A. Delmas and B. Pertuiset, with the collaboration of M. H. Pineau. (Pp. 436; illustrated. £14.) Paris: Masson et Cie. Oxford: Blackwell Scientific Publications. 1959.

Pharmacology. By J. H. Gaddum, M.R.C.S., L.R.C.P., Sc.D., F.R.S. Fifth edition. (Pp. 587+xvi; illustrated. 42s.) London, New York, Toronto: Oxford University Press. 1959.

Never Say Die. A Return to Everyday Living for the Partially Disabled. By Anthony Richardson. (Pp. 107. 12s. 6d.) London: Max Parrish. 1959.

Psychotherapeutic Drugs. By Ashton L. Welsh, M.S., M.D. (Pp. 139+xiii. 36s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Behavioral Analysis. Analysis of Clinical Behavior as applied to Mother-Newborn Relationships. By David M. Levy, M.D. (Pp. 370+xxxiv. 72s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Pathogenesis and Treatment of Parkinsonism. Sixth Annual Scientific Meeting of the Houston Neurological Society, Texas Medical Center, Houston, Texas. Compiled and edited by William S. Fields. (Pp. 372+x; illustrated. 81s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Practical Notes on Nursing Procedures. By Jessie D. Britten, S.R.N. Foreword by George H. Marshall, F.R.C.S.(Edin.). 2nd ed. (Pp. 196+viii; illustrated. 15s.) Edinburgh. London: E. and S. Livingstone Ltd. 1959.

Orthopaedic Nursing. By Mary Powell, S.R.N., M.C.S.P. Foreword by Sir Reginald Watson-Jones, M.Ch.Orth., F.R.C.S., F.R.C.S.Ed.(Hon.), F.R.A.C.S.(Hon.), F.A.C.S.(Hon.) Third edition. (Pp. 464+xii; illustrated. 27s. 6d.) Edinburgh. London: E. and S. Livingstone Ltd. 1959.

Grosse Nervenärzte. Vol. 2. Edited by Kurt Kolle. (Pp. 251+vii; illustrated. DM. 29.40.) Stuttgart: Georg Thieme. 1959.

Cell and Tissue Culture. By John Paul, M.B., Ch.B., Ph.D., M.R.C.P.Ed. (Pp. 261+viii; illustrated. 30s.) Edinburgh, London: E. and S. Livingstone Ltd. 1959.

Guide to Using the Coloured Progress Matrices, Sets A, Ab, B (Revised Order, 1956). Prepared by J. C. Raven, M.Sc. Revised edition. (Pp. 40. 5s.) London: H. K. Lewis. 1958.

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INFLUENZA

Influenza as a clinical diagnosis may include many different infections. The name itself implies no great diagnostic precision, for it was derived from the Italian at a time when the word "influenza" was used to refer to the influence of astral bodies in bringing about visitations. Throughout the centuries since then many a pestilence has gone under this name, especially when the fever has been accompanied by catarrhal inflammation of the throat and bronchi.

There is no mistaking an epidemic of influenza, for no other infection can so suddenly transform the life of a practitioner from busy orderliness to a chaotic nightmare.[1] This evidence is soon supported by a sharp rise in the notifications of pneumonia and in a corresponding increase in deaths among elderly people. When the entirely new Asian virus first attacked the very vulnerable population of this country in the autumn of 1957, the clinical picture was relatively constant. The onset was strikingly sudden, with a rapid rise of temperature to 102°–104° F. (38.9°–40° C.).[2] Acute prostration was characteristic (the patient was often "felled") and was accompanied by aching of the head, back, and limbs; a dry explosive cough with but scanty sputum followed. The chief complication, which occurred mostly in young children and elderly adults, was bacterial pneumonia, with *Staphylococcus aureus* responsible for most of the severe and fatal cases. Only a very small number of these patients developed the fulminating disease so vividly portrayed in the reports of 1918 and 1919.

The first wave of the Asian influenza pandemic spread through this country in August, September, and October, 1957. In many areas children aged 5–14 years were predominantly infected; in one general practice, where a careful survey was made, over three-quarters of the patients were children.[3] When a second wave of infection followed in December and in January, 1958, older people were afflicted. Altogether some 12 million people were affected, with 16,000 deaths, two-thirds of which were in people over 55 years. Clinical attack rates for young people were low in the second wave, and the excess mortality in December and January was probably due to infection of old people with the Asian virus.[4] During the summer and the last months of 1958 there was no indication of any further spread of influenza, and epidemiological evidence suggests that at the beginning of 1959 the young and the old people in the population should be largely immune to the Asian virus.

On the other hand, the position of the population in an economically important age group (20–40 years) must be a matter for some concern, since it seems to have escaped infection by the Asian virus and the consequent immunity. The question must be asked whether this group may bear the brunt of infection in the event of a third wave of Asian influenza. Elsewhere in this issue of the *Journal* (p. 473) Dr. Joan McWilliam has shown that it is just this group of people who lack the specific antibodies to protect them against the Asian virus. The sera were collected in the early autumn of 1958 and her results represent topical information on the trends of immunity of the population in the Edinburgh area. Her findings are in agreement with earlier data collected in the Sheffield area soon after the 1957 epidemic wave.[5]

Some reports on the present outbreak, kindly contributed by general practitioners in response to our invitation, are published at p. 501 this week. They confirm the national statistics that the infection is still very patchily distributed in the country, some areas being free of it, though the infection is epidemic in the London and Birmingham areas and parts of north England; claims for National Insurance benefit are also high in the industrial belt of Scotland. Several of the general practitioners' reports indicate that the infection is not so prevalent among young children and elderly people as it is among older schoolchildren and wage-earning adults. Dr. McWilliam's findings show that this might be expected. Our reporters agree that the infection is in general mild in that complications are few, but that it is disabling and apt to be followed by that disagreeable scourge, post-influenzal debility.

The aetiology of the present wave of "influenza" is not yet clear, since virological diagnostic techniques take longer to give an answer and are more restricted than bacteriological methods. Febrile catarrhs, or the acute respiratory disease ("A.R.D.") often described by American authors, are common at this time of year, and clinically it is not possible to define accurately these illnesses, which may be caused

[1] Pickles, W. N., *Epidemiology in Country Practice*, 1939, Bristol.
[2] Fry, J., *Brit. med. J.*, 1958, **1**, 259.
[3] Woodall, J., Rowson, K. E. K., and McDonald, J. C., ibid., 1958, **2**, 1316.
[4] McDonald, J. C., *Proc. roy. Soc. Med.*, 1958, **51**, 1016.
[5] Clarke, Suzanne, Heath, R. B., Sutton, R. N. P., and Stuart-Harris, C. H., *Lancet*, 1958, **1**, 814.
[6] Progress Report to the Medical Research Council on Trials of an Asian Influenza Vaccine, *Brit. med. J.*, 1958, **1**, 415.

by a wide variety of known (e.g., adenoviruses) and unknown viruses. In many parts of the country there are reports of "influenza" responsible for absence rates in schools of 30–40%, and it seems that some at least of these infections are due to influenza virus B. Particularly striking is the case, reported by Dr. G. I. Watson (p. 502) of a boy who is thought to have had both A and B influenza recently. It is unlikely that the school outbreaks are due to the Asian virus A, since the high incidence of infection in children in 1957 and the high levels of antibody in their sera reported by McWilliam ought surely to imply a protective immunity. So far the tests carried out on material examined at the Central Public Health Laboratory at Colindale show that children are being infected by type B virus, while type A has been found in sporadic cases in adults.

Since influenza is a disease transmitted during close contact by droplet infection, much may be done by common-sense measures of hygiene and ventilation to reduce the risk of infection. More practical still would be the use of a specific vaccine aimed at protecting the individual against the causative virus. If this cause should be either the Asian or the B virus, a vaccine is available which may offer, in an epidemic, a protection rate as high as 60–70%. Even at so late a stage as this the use of this vaccine in so economically important a group as those aged 20–40 might prove useful, since there is evidence that many of them may have a low degree of immunity from earlier inapparent infection, and a single injection of combined A and B virus vaccine should in such cases raise resistance to a level that would give protection within about a week after inoculation. The experience with Asian influenza vaccine given to schoolboys exposed to infection showed that, even when there was no antecedent immunity, a sharp fall in the attack rate occurred in the second week after inoculation compared with a persistently high rate in other groups given injections of influenza B or polyvalent A vaccines.[6]

ORGANIZATION OF MATERNITY SERVICES

The publication of the Cranbrook Committee's Report[1] on the maternity services is an important event, for its recommendations may well have a far-reaching influence on the pattern of the obstetric services of the future. The committee* was set up under the chairmanship of Lord Cranbrook by the Minister of Health in April, 1956, in response to a suggestion by the Guillebaud Committee. The members of that committee were so impressed by the difficulties and complexities engendered by a service whose administration was shared between regional hospital boards, executive councils, and local authorities that they thought the time had come for a comprehensive review of the maternity services in the N.H.S. The Cranbrook Committee was instructed "to review the present organization of the maternity services of England and Wales, to consider what should be their content, and to make recommendations." A parallel committee was appointed in Scotland and is expected to report soon.

The British Medical Association, among others, was invited to give written and oral evidence. The memorandum of evidence which the Association prepared was compiled from the views of a medical committee covering all branches of the profession. Over many of the matters dealt with in the report the opinions of the Cranbrook Committee are in harmony with those put forward by the B.M.A., although the emphasis may differ here and there. The report, like others before it, rightly stresses the importance of co-operation between the various branches of the medical profession in providing for the needs of the expectant mother during pregnancy and parturition. This co-operation, it says, should also extend between doctors, midwives, and local authorities; and it should be strengthened by the establishment of professional liaison committees, by the encouragement of clinical contacts between general-practitioner obstetricians and obstetric specialists at hospitals, and by an exchange of clinical information between all parties concerned with the care of the patient, which should ensure, among other things, that the family doctor is fully aware of what is happening to his patient.

Taking the country as a whole, the report puts forward as an optimum figure the provision of sufficient maternity beds to accommodate 70% of mothers for their confinements, and lays particular stress on the need for antenatal beds (the number of which should equal 20–25% of all confinements in the area) and also for beds for the general-practitioner obstetrician. The report recommends that the extra beds needed to bring the figure up to 70% of confinements should, where possible, be general-practitioner beds. All this will be generally welcomed, and it is to be hoped that boards of governors and regional hospital boards will be asked to make a critical survey of the maternity hospitals and units which they administer to ensure that the number of beds is adequate and that general-practitioner obstetricians have access to beds. The provision of additional antenatal beds should have priority.

*The medical members of the committee were: Dr. A. Beauchamp, Mr. G. F. Gibberd, Dr. W. V. Howells, Dr. Jean Mackintosh, Mr. H. J. Malkin, and Dr. J. Forest Smith.

[1] Ministry of Health, *Report of the Maternity Services Committee*, 1959. H.M.S.O., London. Price 6s. 6d. net.

The committeee has given a good deal of thought to the possibility of unifying the present tripartite administration under a single authority. Cumbersome and complex as the present arrangement is, the members felt that to alter one part of the service, leaving the others as they are, would create more problems than it would resolve, and that it was wiser not to disturb present arrangements. The committee was impressed by the value of health education provided at the clinics of local authorities, but came to the conclusion that the general-practitioner obstetrician should ultimately replace the local authority's medical officer in providing maternity care in local-authority antenatal clinics.

While most of the report will probably be acceptable to consultant obstetricians, general practitioners are likely to have serious misgivings about some of the recommendations affecting their function in the maternity service. In its evidence to the committee the B.M.A. emphasized the opinion often expressed in the Representative Body that all general practitioners who wished should be able to undertake midwifery in the N.H.S. and be paid for the work they do. In 1948 the Association agreed, reluctantly, to the establishment of the "obstetric list" and a scale of fees for maternity work, differentiating between those on the list and the rest. However, the Association's view now is that the list and the differential fee should be abolished —or if there must be a list it should merely be used to indicate those doctors who wish to practise midwifery, and admission to it should be automatic on application. The Cranbrook Committee, while supporting an increase of fees to the G.P. on the obstetric list, wishes not only to retain the list but also to tighten up the criteria for admission to it. It insists on a six-months resident appointment in an approved maternity unit as an essential qualification, and on a three-yearly review of the list and automatic exclusion from it if the amount of maternity work done during the preceding three years falls below a specified amount (an average of 20 cases a year). Doctors not on the list are to receive no fee at all for maternity work done for patients on their N.H.S. list.

Surely, if it is desirable to continue with the obstetric list and to insist on rigid criteria of this nature, it would be more logical to ensure that the young doctor who has passed his finals could qualify for the obstetric list in his pre-registration year. One possible method would be to establish rotating internships of 12 months' duration in which the young doctor would spend four months each in the departments of medicine, surgery, and obstetrics as a resident medical officer. It could then be left to each doctor to decide, on entering the service, whether to go on the obstetric list or not. If the intention of the committee is to exclude from the practice of midwifery doctors who cannot satisfy the criteria for admission to the obstetric list, then the committee's proposals must be looked at in the light of the requirements of the General Medical Council which have to be fulfilled before registration. There is no power which can prohibit a legally qualified and registered practitioner from engaging in midwifery practice for his N.H.S. patients. Since midwifery is not part of the duties specified under his contract with the N.H.S., it would be logical that the State should allow him to charge his N.H.S. patients private fees for his service if no payment is forthcoming from the N.H.S.

The report also advocates consultant supervision of the work of general-practitioner maternity units, but with reservations, so as not to trespass too closely on clinical freedom. In practice this sort of supervision is most difficult to achieve, and is likely to end in being purely nominal and ineffective or else to be regarded as unwarranted interference with the general practitioner's clinical control of his patient. It would be better to maintain the time-honoured relationship between general practitioner and consultant, in that the general practitioner remains in sole and undisputed charge of his patient, while always being able to call on the full range of consultant and ancillary services. As Mr. S. Bender remarks in an article at p. 497 in this issue, the family doctor most commonly calls the consultant obstetrician to a consultation in the patient's home because he feels that "with some specialist help and advice he himself could retain clinical control of the particular case."

TWO NEW STEROID EFFECTS

A considerable number of variants have now been made to the cortisone molecule, often with much improvement in its therapeutic action, and the main desirable and undesirable results of these are becoming well known. But the strong possibility remains that other types of naturally occurring steroids may be found with quite different effects. Two examples of such developments have recently come to light.

First, a group of workers at the Sloan-Kettering Institute for Cancer Research, New York,[1] has found

[1] Kappas, A., Hellman, L., Fukushima, D. K., and Gallagher, T. F., *J. clin. Endocr.*, 1958, **18**, 1043.
[2] Prader, A., Spahr, A., and Neher, R., *Schweiz. med. Wschr.*, 1955, **85**, 1085.
[3] Luetscher, J. A., Jnr, and Curtis, R. H., *J. clin. Invest.*, 1955, **34**, 951.
[4] Neher, R., Desaulles, P., Vischer, E., Wieland, P., and Wettstein, A., *Helv. chim. Acta*, 1958, **41**, 1667.

that etiocholanolone has potent activity in raising body temperature. Etiocholanolone is one of the principal urinary ketosteroids, being a degradation product of several hormones derived from both the testis and the adrenal. These American workers found that when purified samples of this well-known metabolite were injected intramuscularly into human subjects, they caused a sharp rise of temperature, usually to above 103° F. (39.4° C.). The reaction was prompt and reached its maximum in nine hours, after which a rapid defervescence ensued. There was an associated leucocytosis. It was shown that this curious reaction was not due to pyrogenic impurities either in the steroid or in the solvent used. The effect was remarkably specific and was not produced, for instance, by the 3-β-hydroxy epimer, which was completely inert. After injection of the steroid, the greater part of it could be recovered within the next 24 hours from the urine, showing that little transformation to another compound takes place in the body. When the etiocholanolone was given in small doses daily, a continuing fever could be produced which persisted until injections were discontinued. There was no evidence of the development of any tolerance.

What the significance of this thermogenic action may be it is at present difficult to say. The workers have found that the corresponding C_{21} steroid pregnanolone also has similar pyrogenic action, and it may be that the slight but definite thermogenic effect of progesterone is caused by degradation to metabolites of this type. If so, then the normal rise in body temperature after ovulation may be due to the products of progesterone metabolism.

The other new steroid action comes from a different source. It has been recognized for some years that the sodium-excreting activity of the human kidney could not be explained solely in terms of aldosterone. Thus the patient with Addison's disease is much more sensitive to the sodium-retaining effects of D.C.A. (cortexone) than the normal person, and even large doses of D.C.A. in normal subjects may fail to produce excessive retention of sodium. The possibility is recognized of the existence of a sodium-excreting factor which could counteract the effects of the D.C.A. Another clue pointing in the same direction came from the study of cases of congenital adrenal hyperplasia. Some of these patients, who are unable to produce hydrocortisone, lose excessive salt in the urine. It was natural to suspect that this electrolyte defect was due to an additional inability to produce aldosterone. But recently two groups of workers[2,3] have shown that these subjects have more than normal amounts of aldosterone in the urine. Since lack of aldosterone therefore could not account for the sodium-losing state, an alternative possibility was the excessive secretion of a sodium-excreting factor among the products of the overactive adrenal.

An extensive and careful search for such a compound has now been made by a group of Swiss workers.[4] By a series of chromatographic separations they were able to obtain from the urine of a 5-year-old patient with congenital adrenal hyperplasia a crystalline product which, when tested in animals, had the property of increasing excretion of sodium by the kidney. Because of the difficulty of obtaining sufficient urine from such subjects, a large-scale attempt was made to obtain this new substance from hog adrenals. 2,000 kg. of such glands were used as the starting material, and from this bulk of tissue a crude extract was prepared. After concentration to a weight of about 440 g., it was submitted to paper chromatography on a very large scale, 3,800 sheets being used in the first stage. From these the active zones were eluted and were again run on a further 400 sheets of paper. By eluting once again the active substance from these sheets, a final yield of 54 mg. of an interesting steroid was obtained. After allowing for losses, the content was estimated to be 30 mg. per 1,000 kg., or 30 parts per million.

With striking promptness the chemical formula of this compound was worked out to be 3-β-16-α-dihydroxy-allopregnan-20-one. Two points are of special interest about this formula. First, we have a compound possessing hormonal activity which is not unsaturated in ring A, and secondly the attachment of a hydroxyl group to the carbon 16 has already been found to influence profoundly the electrolyte activity of synthetic steroids. It is the presence of this 16-hydroxyl in triamcinolone, for instance, which has almost completely eliminated the undesirable sodium-retaining effect from this steroid.

The pharmacology of this new natural steroid has not yet been worked out. It appears to act as a sodium-excreting factor, but only under certain conditions which have not yet been properly defined. Until these conditions are better clarified the new steroid is not likely to be suitable for therapeutic trial. But it has already been synthesized by several different methods, and we may hope that this steroid will prove to be the forerunner of further synthetic steroids of similar type which have more potent sodium-excreting action, for there is a need for such a substance in therapeutics. The recognition of such a hormone would probably go far to clarify much that still remains obscure in the pathogenesis of many forms of oedema.

VIEWS OF JUVENILE DELINQUENTS

The Wolfenden Committee expressed regret that no prostitute had been found willing to give evidence, and it seems unlikely that the Ingleby Committee, now sitting to advise among other matters on the procedure and work of juvenile courts, will be able to secure at first hand the views of young delinquents. However, Dr. Peter Scott, a member of this committee, has managed to gain some idea of what this section of the population thinks about juvenile courts, and his report[1] largely lets the young criminal speak for himself with a minimum of comment.

Boys in a remand home in 1957 were asked by the head teacher during class-room activities to write anonymous accounts of "What Happened to me in Court." Over a hundred essays were obtained, mostly from boys who were offenders, some truants, some "beyond control," and "care or protection" cases. Some were first offenders but many were experienced in court procedures. All the boys were between 12 and 16 years. In general only a small proportion seem to have understood quite clearly what was going on in court—a small number whose account of what happened was entirely coloured by their strong emotions, and a majority who just accepted the procedure without understanding or questioning what it was all about. They appeared to be interested only in their "sentence"—a significant description of the order of the court where the welfare of the child is supposed to be a dominant consideration and retribution of secondary concern: the remand home boys thought otherwise.

There were many interesting comments on the personnel of the court, but apart from clearly identifying the chairman of the bench—usually as "the judge"—there was great confusion between ushers, clerks, and even what was described as the "jury" (probably meaning the balance of two magistrates on the bench).

It is a justifiable criticism that many courts are too crowded and also that waiting is often too long, and the waiting accommodation and facilities may be shocking. In general the boys wrote more about what went on outside the actual court-room than about the court, and this seems a clear point for urgent reform.

An analysis of the attitude of boys in court to the reports received, the fairness of the bench, and their general reactions brings out clearly the effect of the home background. A one-sentence essay from a boy with a very hostile home background began with the words, "I think the courts stinks." Dr. Scott warns magistrates that antagonism or docility shown by their clients should not be interpreted too literally. Many of the children are far too disturbed to take in anything that happens or to listen, probably, to any helpful remarks from the chairman. The police often refer to the fact that juveniles leave the court with little or no respect for the magistrates, and experienced magistrates admit that the attitude of their clients is often one of genial contempt.

It is perhaps unwise to judge too much by the immediate superficial reaction of a young delinquent to his visit to the court, but equally there is a strong case for a stricter and more formal attitude in court, especially for the older "young persons" group. Better waiting accommodation would help, and, if local authorities are really serious in wanting to improve measures to help problem families and potential adult delinquents in their early years, they could usefully spend some money on better court facilities.

NEEDLE BIOPSY OF THE LIVER

Since the introduction by P. Iversen and K. Roholm[1] of percutaneous needle biopsy of the liver as a routine diagnostic procedure, it has been widely used and given much information on liver pathology as well as greatly improving the accuracy of diagnosis. The method spares the need for laparotomy and surgical biopsy, which is all the more important because specimens obtained at surgical biopsy are of necessity subscapular and not representative of the main mass of the liver. For example, a specimen taken from the inferior edge may show cirrhosis even though the liver as a whole is normal.

Unfortunately, needle biopsy of the liver is not without risk to life, though the risk is small. N. Zamcheck and O. Klausenstock[2] reviewed the risks in just over 20,000 examinations reported in the literature and found 34 deaths, giving a fatality rate of 0.17%. This agrees closely with a smaller collection made by R. Terry[3] in which the fatality rate was 0.12%. The usual cause of death was haemorrhage due to laceration of the liver. This risk can be kept small by ensuring that the procedure is carried out only by those who have studied the technique and who keep in good practice at it. The risk can be further reduced by not carrying out the procedure in any patient who is in a potentially haemorrhagic state, such as when the prothrombin value of the blood is grossly diminished.

That there still remains room for further improvement is apparent from a recent report by C. J. Fisher and W. W. Faloon[4] on 341 patients in whom liver biopsy was carried out by means of the Vim-Silverman needle. There were five deaths due to intraperitoneal haemorrhage (1.5%), even though no biopsy was performed unless the prothrombin activity of the blood was at least 60% of normal and though none was performed in the presence of severe anaemia or of any known haemorrhagic disorders. The striking finding was that four of the deaths occurred among 33 patients suffering from metastatic malignant disease of the liver. In other words, the risk among this subgroup was high (12%) compared with a low rate (0.3%) among the remainder. Fisher and Faloon therefore conclude that the type of liver disease present has a bearing on the

[1] *Brit. J. Delinq.*, 1959, **9**, 200.

[1] Iversen, P., and Roholm, K., *Acta med. scand.*, 1939, **102**, 1.
[2] Zamcheck, N., and Klausenstock, O., *New Engl. J. Med.*, 1953, **249**, 1062.
[3] Terry, R., *Brit. med. J.*, 1952, **1**, 1102.
[4] Fisher, C. J., and Faloon, W. W., *Amer. J. Med.*, 1958, **25**, 368.
[5] Menghini, G., *Gastroenterology*, 1958, **35**, 190.

risk of needle biopsy and suggest that laparotomy and surgical biopsy should be carried out if metastatic malignant disease is suspected. This suggestion does not appear to be a perfect solution to the problem, because a diagnostic method ought to be usable when the diagnosis is completely unknown. Perhaps a more satisfactory solution is to improve the actual technique of the biopsy and reduce the risk by this means. A promising example of this approach is the method devised by G. Menghini,[5] in which the duration of the intrahepatic stage of the biopsy is reduced to a fraction of a second. The reduction to a minimum of the time spent with the needle in the liver substance is of obvious importance in lowering the risk of laceration of the liver through the patient inadvertently breathing during this part of the procedure.

HYPERCALCIURIA

The relationship between dietary intake of calcium and urinary excretion in normal subjects was examined in detail by E. L. Knapp more than ten years ago.[1] Two principal conclusions can be drawn from her work: first, the apparent variation between individuals on the same diet can be greatly reduced by taking body weight into account; secondly, the mean calcium excretion of normal subjects is relatively slightly influenced by diet, although there are a few whose excretion rises steeply with a rising intake. The first of these findings is seldom applied by workers in this field, who still tend to express the output of calcium in the urine as "mg. per day," but the second has been amply confirmed.[2,3] It is therefore surprising how commonly it is considered necessary to put patients on low-calcium diets before any attempt is made to measure their urinary output of calcium.[4]

A. Hodgkinson and L. N. Pyrah[5] have now performed a useful service in assembling a large quantity of data from the literature and comparing it with their own observations on normal subjects and on patients with renal calculi. The conclusion they reach is that, on a diet containing about 600–1,000 mg. of calcium, 90% of normal men excrete less than 300 mg. daily and 90% of women excrete less than 250 mg. daily. They make no attempt to define more precisely the upper limit of normal calcium excretion on this diet, but they report that 37% of male and 14% of female patients suffering from renal calculus but having normal renal function excreted more than 300 and 250 mg. calcium daily respectively on this "normal" diet.

Hodgkinson and Pyrah have also measured the urinary calcium in 32 patients with renal calculus both on the ward diet and on a diet containing about 150 mg. calcium. 14 of these patients had abnormally high values of urinary calcium (as defined above) on the ward diet and 16 excreted more than 175 mg. daily on the low-calcium diet. Since a survey of the literature had shown that 90% of normal adults excreted less than 175 mg. calcium daily on a low-calcium diet, they concluded that there was "reasonable agreement" between the proportion of cases with excessive urinary calcium as revealed by the two diets.

Though this work has brought us nearer to a working definition of hypercalciuria, and has shown that it can frequently be diagnosed on a ward diet, it has shed no light on the physiological mechanism at work nor on the significance of the condition. Hypercalciuria is, of course, an almost invariable accompaniment of hypercalcaemia, unless renal function is impaired, but it is associated with a normal calcium level in the serum in states of metabolic acidosis; in these circumstances it might well be termed "secondary hypercalciuria." However, there are some subjects, such as those referred to above, whose urinary calcium is high for no apparent reason and to whom the term "primary hypercalciuria" might reasonably be applied. This classification would permit the use of the term "idiopathic hypercalciuria" to be confined to a particular syndrome recently defined by the team at the Massachusetts General Hospital.[6]

F. Albright and his colleagues[7] first attached the term idiopathic hypercalciuria in 1946 to a case of osteomalacia which they tentatively attributed to the excessive loss of calcium in the urine. (The patient was also suffering from steatorrhoea, so this might have been the cause.) A further report[8] from this team showed that the syndrome included hypophosphataemia. The latest work from the same source[6] provides further data on 35 cases and defines the condition as being characterized by a "normal serum calcium level, a low serum phosphate level and an increased urinary calcium excretion." All the patients in this series presented with renal stones, and only by their serum calcium levels were they biochemically distinguishable from patients with primary hyperparathyroidism. But in 11 of them exploration of the neck had been negative, and the fact that all 32 cases were males tells against a diagnosis of parathyroid adenoma. In three of the patients the hypercalciuria was found to persist on a low-calcium diet, but the faecal calcium was found to be abnormally low. In 10 of them the urine calcium was appreciably lowered by the oral administration of sodium phytate.

This latest work from Boston prompts many questions. It would be interesting to know whether any of the patients were suffering from osteomalacia or osteoporosis; the rate of tubular reabsorption of phosphate; the effect of calcium infusion upon the latter,[9] and the level of ionic calcium in the plasma.[10] In the absence of such information it is possible only to speculate on the cause of idiopathic hypercalciuria: perhaps cases of renal calculus may exist in which primary parathyroid overactivity is not reflected in any anatomical change in the parathyroid glands.

[1] Knapp, E. L., *J. clin. Invest.*, 1947, **26**, 182.
[2] Nicolaysen, T., Eeg-Larsen, N., and Malm, O. J., *Physiol. Rev.*, 1953, **33**, 424.
[3] Steggerda, F. R., and Mitchell, H. H., *J. Nutr.*, 1951, **45**, 201.
[4] McGeown, M. G., *Clin. Sci.*, 1957, **16**, 297.
[5] Hodgkinson, A., and Pyrah, L. N., *Brit. J. Surg.*, 1958, **46**, 10.
[6] Henneman, P. H., Benedict, P. H., Forbes, A. P., and Dudley, H. R., *New Engl. J. Med.*, 1958, **259**, 802.
[7] Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., and Roos, A., *Medicine (Baltimore)*, 1946, **25**, 399.
[8] —— Henneman, P., Benedict, P. H., and Forbes, A.P., *Proc. roy. Soc. Med.*, 1953, **46**, 1077.
[9] Nordin, B. E. C., and Fraser, R., *Clin. Sci.*, 1954, **13**, 477.
[10] Fanconi, A., and Rose, G. A., *Quart. J. Med.*, 1958, **27**, 463.

Drug Treatment of Disease

TREATMENT OF CORYZA

BY

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Though there is still no cure for the common cold, something can be done to mitigate its evils. But the important advances in chemotherapy during the present century have produced no effective drug to shorten the course of this widespread affliction. In 1810 Dr. E. Bullman, in his *Medical Directory or Family Physician*, advised his lay readers that "the cure consists as much in regimen as in medicine," a statement which applies equally to-day. Indeed, the best advice is that patients with coryza should confine themselves to their own homes, remaining in an even temperature, though not necessarily in bed, until the symptoms have abated. Unfortunately this course, which would shorten the patient's distress and prevent widespread dissemination of winter colds, is seldom followed. Most patients, following the example rather than the advice of their doctor, continue to regard the common cold as a trivial annoyance rather than an illness. Thus they remain at work, with an air of martyrdom, spreading the germs of disease among their fellow men.

Many remedies have been advocated for the cure of colds, and the medical profession has not been blameless in introducing and popularizing some of these alleged cures. But in the treatment of an illness which naturally lasts only three or four days it is easy to attribute curative properties to any drug—especially if introduced on the second or third day. Moreover, in giving treatment for a disease of such short duration it is exceedingly difficult to assess the results of new drugs. Too seldom are such remedies put to statistical trial. It can be safely said, however, that no remedy put to scientific test has proved its worth in shortening the course of the illness. Treatment remains largely symptomatic.

Vaccines

Ideally the aim should be to prevent infectious diseases by protective inoculation and by public health measures. Coryza is a virus disease, and no effective vaccine has so far been introduced for its prevention. Anticatarrhal vaccines have been popular for many years. These are bacterial vaccines, prepared from organisms known to invade or inhabit the upper respiratory tract. They are valueless in preventing colds: their action, if any, is in preventing secondary bacterial infection. In particular, they may be helpful in the management of patients prone to severe bronchitis after colds. In these patients anticatarrhal vaccine is worth trying, but the results are so variable as to cast doubt on its true value. The vaccine is given in three doses, 0.25 ml., 0.5 ml., and 1 ml., at weekly intervals. It is best given in October, but, since it is claimed that immunity lasts only for three months, a second course should be given in January. Vaccines for oral administration have been introduced, but there is no evidence of their efficiency.

Imbibing large quantities of various vitamins has been advocated for the prevention of winter infections. True as it may be that infections are common in cases of vitamin deficiency, there is no evidence that oil-soluble vitamins or vitamin C protects individuals of normal dietary habits from the common cold. Avoiding contact with infection is impracticable in modern civilization, where crowded buses and trains, communal life in factories, and visits to the cinema are all part of the daily routine.

Antibiotics and Sulphonamides

It is not unnatural that antibiotics have been used in the treatment of the common cold, since they have a powerful effect in suppressing secondary infection. It has even been asserted that broad-spectrum antibiotics should be given as a routine in the treatment of coryza. Not only are the claims that antibiotics shorten the course of the illness without foundation, but there are serious objections to their use. There is the risk of toxic effects from the antibiotics, such as drug sensitization, gastro-intestinal upsets, and even, in the case of chloramphenicol, possibly fatal agranulocytosis. There is also the risk of encouraging overwhelming respiratory, general, or gastro-intestinal infection with drug-resistant staphylococci. Although numerically slight, these grave risks must be weighed against the trivial and benign course of the disease. A final objection to the routine use of antibiotics is the expense to the nation.

If antibiotics are to be used for the control of secondary infection they should be withheld, as a rule, until the signs of secondary infection appear. But there are circumstances in which antibiotics justify their use in the early stages of coryza. Patients with chronic or recurrent infection of sinuses, and children with recent or recurrent middle-ear infection, should receive antibacterial treatment early. Since the invading organisms are usually pneumococci or streptococci, either a sulphonamide or penicillin should be adequate. Sulphadimidine, 1 g. three times daily in tablet form for adults, or in a palatable suspension for children (mist. sulphadimidin. pro. inf. *B.P.C.* contains approximately 0.5 g. in each dose), should be given for four or five days. If penicillin is given, oral administration is sufficient, and is certainly more acceptable to the patient and more convenient to the busy family doctor than repeated injections. Phenoxymethylpenicillin (penicillin V) is probably the most reliable oral preparation, 60 mg. being equivalent to about 100,000 units of penicillin. The tablets should be given half an hour before meals and at not longer than four-hourly intervals, but doubling the last dose at night avoids interrupting sleep. The dose for adults is 125 to 250 mg. four-hourly, for children 62.5 to 125 mg., and for infants 30 to 62.5 mg.

In patients with bronchiectasis or with chronic bronchitis and respiratory impairment, antibiotics will often prevent severe and prolonged episodes of respiratory infection and lessen the risk of further damage to the lung. Here, a four- or five-day course

of one of the tetracyclines is probably the treatment of choice, since *Haemophilus influenzae* often predominates in producing secondary infection. Tetracycline itself, chlortetracycline, or oxytetracycline are the most suitable drugs; the dose in each case being 250 mg. four times daily.

Analgesics

Aspirin is an excellent drug for relieving malaise and reducing fever. The indiscriminate swallowing of whole aspirin tablets is to be deprecated, since it is a cause of severe gastro-intestinal bleeding. Soluble aspirin is preferable, one to three 5-gr. (320-mg.) tablets being dissolved in water before swallowing. This dose may be repeated six-hourly. Aspirin, combined with Dover's powder (tab. acid. acetylsalicyl. et opii co. *B.N.F.*) is a more powerful diaphoretic and analgesic than aspirin alone. Up to four tablets may be taken at a time. There is no experimental evidence that alcohol is beneficial, but tradition justifies the use of hot whisky and lemon, if so desired, as a "night cap."

Inhalations

Steam inhalations are of inestimable value in relieving nasal and laryngeal congestion in the early stages of a cold. Benzoin and menthol, either alone or in combination, are the most popular preparations. Their action is partly due to the inhalation of steam, and they should not be used immediately before going into the cold air. Proprietary pocket inhalers containing aromatic vasoconstrictors have achieved some popularity. Amphetamine is no longer used in inhalers, since it was found that many patients became addicted to its use. Inhalers containing propylhexedrine are available. This drug has a less vasoconstricting action than amphetamine, but it is not habit-forming. Apart from convenience, these pocket inhalers have no advantages. Their use should be discouraged on the grounds that a patient whose cold is severe enough to require repeated inhalations is ill enough to be at home having adequate treatment and infectious enough to stay away from work.

Nasal drops and sprays should be used with care. In no circumstances should oily solutions be administered. Not only do these preparations impede the helpful ciliary action of the nasal mucosa, but there is a risk of their being inhaled into the lungs, where they may cause extensive and severe lipoid pneumonia. Drops containing sulphonamide and antibiotics are of limited value and open to the dangers referred to earlier. After using nasal sprays, patients tend to clear the nose by vigorous blowing, but this may help to spread infection into the paranasal sinuses and middle ear.

Vasoconstriction by means of a 1% solution of ephedrine in saline (narist. ephed. *B.N.F.*) alleviates nasal congestion and is the simplest and safest of the many popular preparations. A simple alkaline douche such as solv. nasal. alk. *B.N.F.* is helpful in clearing the nose at a later stage; again, the patients should be warned against enthusiastic nose-blowing after use.

Gargles

Gargles have been used extensively in the past for the treatment of the pharyngitis accompanying upper respiratory infections. Although they are possibly beneficial when the tonsils are enlarged, it is difficult to see how they can benefit the patient with pharyngitis, since the fluid does not get beyond the anterior faucial pillars during the act of gargling. To be effective, the preparation should be swallowed after gargling. Garg. ferr. perchlor. *B.N.F.* or glycer. thymol. co. *B.N.F.* can be used in this way. If relief from painful swallowing is needed, lozenges are probably preferable. Troch. benzocain. co. *B.N.F.*, containing benzocaine and menthol, acts as a pleasant local anaesthetic, but has the slight disadvantage of anaesthetizing the tongue and spoiling taste at the same time. Incorporating antibiotics in gargles and lozenges is valueless and possibly dangerous in the treatment of patients with coryza.

Antihistamines

Antihistaminic drugs have been widely advocated in the treatment of coryza, but without justification. Although highly effective in controlling rhinorrhoea in hay fever and, to a less extent, in perennial vasomotor rhinitis, antihistaminics are useless in the treatment of the common cold.

General Aims

Until successful prophylactic measures are discovered, the common winter upper respiratory infection will continue to be a burden to the community and the practitioner. At present there are no effective means of control and treatment is largely palliative. The doctor's aims are to ease the patient's symptoms, to avoid accepting the diagnosis of coryza too readily in febrile illness in the winter, to try to persuade the patient to keep the infection to himself, to give effective antibiotic treatment in occasional cases, and finally to refrain from exposing the patient to risks of treatment which might be more formidable than the disease.

OBSTETRIC PROBLEMS OF THE GENERAL PRACTITIONER

AS SEEN BY A CONSULTANT

BY

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The problems of the general practitioner in domiciliary obstetrics are quite different from those of his specialist colleague working in hospital. For example, a sharp ante-partum haemorrhage or a severe toxaemia may tax the skill and resource of the obstetrician in an institution, but to the general practitioner such a case poses no real problem; the disposal of the patient is obvious—after appropriate first-aid treatment she must be transferred to hospital.

The real problems of the general practitioner obstetrician are shown by the three sets of circumstances in which he calls in a consultant to see the patient outside hospital. First, the specialist may be summoned to help in an acute emergency, most often in labour, such as delay in the second or third stage. Secondly, the family doctor may call in the consultant as a reinforcement, where he himself has strongly advised the patient to enter hospital but she has refused. In three cases in this series the patient rejected such advice from both general practitioner and specialist. Thirdly, and by far most commonly in my experience, the consultant is

called because the family doctor feels that with some specialist help and advice he himself could retain clinical control of the particular case, without transfer of the patient to hospital and without added risk to mother or baby.

In an attempt to define these problems a review is made of 244 consecutive consultations outside hospital in connexion with women 28 or more weeks pregnant. The period of review was the three and a half years ending on June 30, 1958. The cases fell naturally into three groups—namely, ante-partum, 158 cases; intra-partum, 63 cases; and post-partum 23 cases. The first group out-numbered almost by two to one the other two groups combined. Of the 244 women, 123 (50%) were transferred to hospital sooner or later.

The complications in each group for which consultations were sought are shown in Tables I, IV, and V. In regard to the most common, the questions asked by the general practitioners are given, together with the courses of action taken and the results obtained. If the standards of antenatal care and intra-partum management by the family doctors were not always of the highest, the judgment and technique of the specialist was not always faultless. And naturally the views and practice of the consultant, whose previous experience had been largely confined to hospital obstetrics, underwent some change as his experience of domiciliary midwifery increased.

Ante-partum Consultations

Ante-partum consultations were requested for no fewer than 14 different conditions (Table I), but two complications of pregnancy accounted for almost 60% of the total cases in this group. These were post-maturity and toxaemia; they, together with spontaneous premature rupture of the membranes, are discussed further.

TABLE I.—*Ante-partum Consultations* (158 *Cases*)

Post-maturity	47	Rh-isoimmunization	4
Toxaemia	46	Thrombophlebitis	3
Mild ante-partum haemorrhage	16	Depressive state	3
Malpresentation	10	Intrauterine death	2
Premature rupture of membranes	9	Disproportion	2
Abdominal pain	9	Acute vulvovaginitis	2
Vomiting	4	Hypotension	1

Post-maturity

General practitioners were perplexed because they knew that some obstetricians regarded post-maturity as a serious and not uncommon problem, while others thought it of little or no account. The questions the family doctors asked me could be summarized as, "Action or inaction?" and, "If action, where, when, and how?" The two conditions in which the family doctor is most often subjected to pressure and agitation by the patient and her relatives are prolongation of pregnancy and delay in labour.

Statistics can be produced from different hospitals showing that good results and bad results have attended policies both of intervention and of non-intervention for post-maturity. But conditions in different hospitals, or in the same hospital at different times, are not always strictly comparable, and ideally the best test would be to try both policies in the same hospital at the same time. This was done by Racker *et al.* (1953), and their figures showed that a lower perinatal loss accrued from a policy of intervention. It is probably also significant that when an obstetrician has changed his views it has nearly always been from complacency to concern. In this series, generally but not routinely, action was advocated; the decision to induce or not being made on the sum total of all the evidence, including the age and previous obstetrical history of the patient.

The method of induction most often employed was tapping of the hindwaters, reinforced in some of the earlier cases by the injection of 1 unit of oxytocin intramuscularly half-hourly up to a maximum of six doses. The Drew Smythe catheter has certain advantages in these cases. The amount of liquor amnii in the forewaters is small in most cases of true post-maturity, especially when the head is deeply engaged; rupture of the forewaters is therefore less likely to be followed by the rapid onset of labour. Tapping the hindwaters allows a greater amount of liquor to be released and also permits a better assessment of the quality as well as the quantity of fluid in the amniotic sac. This is important because if the amount of liquor is very small, or if the fluid resembles thick pea-soup, or both, the foetus is probably already suffering from a serious degree of hypoxia and should be delivered quickly, even if this necessitates caesarean section.

The results in the 47 cases were satisfactory in that there was no perinatal mortality (Table II). However, three of the babies had birth weights of less than 5½ lb. (2,500 g.), which may indicate either errors of judgment or evidence that even in prolonged pregnancy the foetus may be technically "premature." Only 10 of the 47 women were transferred to hospital. In 12 of the remainder the presumptive diagnosis of post-maturity was not considered correct; in the absence of other complications no active measures were taken, and all 12 later started in labour spontaneously and were delivered uneventfully at home.

TABLE II.—*Results in* 47 *Cases of Post-maturity*

Active treatment at home	32	No active treatment at home	15
Delivered at home	25	Delivered at home	12
Delivered in hospital	7	Delivered in hospital	3
Failed induction	4 (1 C.S.)	Breech presentation	2
Scanty thick liquor	2 (1 C.S.)	Elderly primigravida	1
Prolonged labour	1		

Perinatal mortality, nil. Premature babies, 3.

Toxaemia

Here the question asked was, in effect, "Which cases of toxaemia can be safely supervised at home?" The general practitioner appreciated that severer degrees of toxaemia required treatment in a specialist-staffed hospital, but he would have preferred to supervise the milder cases at home. In this series the advice given was that only those women with a mild uncomplicated essential hypertension in pregnancy were suitable for supervision outside hospital, and even these patients were best booked for delivery in a specialist-staffed maternity unit and admitted there two weeks before the expected date of labour.

In all other types and degrees of toxaemia the march of the condition was considered so unpredictable that the constant supervision obtainable only in an institution was desirable. And it was pointed out that the woman with a mild hypertension allowed to remain at home must be closely watched against the supervention of pre-eclampsia. Such supervention, indicated by a rise in blood pressure and by the appearance of albuminuria, necessitated the immediate transfer of the patient to hospital because it added so greatly to the hazards for both mother and baby.

Spontaneous Premature Rupture of Membranes

The family doctor found the disposal of patients with this complication difficult to decide. The questions asked were, in effect, "Action or inaction?" "Home or hospital?" and "Antibiotics or not?" In answering these questions the figures quoted by Eastman (1956) were heeded, a distinction being made between the mature and the premature baby. Eastman drew the dividing line at 2,500 g. (5½ lb.) birth weight, but as this cannot be ascertained before delivery the distinction was here made arbitrarily at 37 weeks' gestation.

Eastman's figures (Table III) showed that the perinatal mortality in *mature* babies was quadrupled if more than 48 hours elapsed between spontaneous rupture of the membranes and onset of labour. The perinatal loss in *premature* babies was largely determined by the degree of prematurity.

TABLE III.—*Perinatal Mortality in Spontaneous Premature Rupture of Membranes (after Eastman, 1956)*

	Labour Started	Perinatal Mortality
2,615 mature babies	In 80% within 24 hours „ 90% „ 48 „	1·7% when interval *less* than 48 hours 6·8% when interval *more* than 48 hours
540 premature babies	„ 50% „ 24 „ „ 70% „ 48 „	Determined largely by degree of prematurity

If, therefore, the baby was adjudged *mature*, and excluding any additional complication—for example, malpresentation, cord prolapse—the onset of labour was expedited. Initially, measures were taken to this end in the patient's own home, 1 unit of oxytocin being injected intramuscularly every half-hour to a maximum of six doses. This was done on the understanding that if labour did not start within six hours of the last injection the patient would be transferred to hospital for an oxytocin drip. Antibiotics were not given while the patient was at home, but after admission to hospital they were administered in the interests of both mother and baby (Smith *et al.*, 1956; Bound *et al.*, 1956).

If, however, the foetus was adjudged *premature*, active measures were not taken, because here prematurity was the outstanding cause of perinatal loss. But admission to hospital was urged so that the facilities of the premature-baby nursery would be immediately available if required. Antibiotics were regarded as necessary because of the low resistance of the premature baby to infection and because the mother was in a strange bacterial environment. If labour did not start within 72 hours of admission and liquor was no longer draining, the antibiotic therapy was discontinued and the patient was allowed home the next day. The perplexing cases were those in which liquor continued to drain in quantity for weeks or even months. The pathology of this condition has been discussed by Burnett (1957). "Masterly inactivity" is probably the best policy, but there is a somewhat greater than average incidence of foetal abnormality in these pregnancies.

Of the nine cases of spontaneous premature rupture of the membranes in this series two babies were lost, both being instances in which the principles laid down above were not closely followed. A mature baby died *in utero*; the patient had not been transferred to hospital when active measures outside failed to initiate labour. A premature baby died from septicaemia 72 hours after delivery in hospital; the mother had not been given antibiotics in labour.

Intra-partum Consultations

Almost two-thirds of the 63 calls during labour were on account of delay (Table IV). Prolongation of each of the three stages of labour is discussed further.

In none of the 10 parturients in whom possible disproportion was the indication for consultation was this complication present; all were delivered at home without foetal loss. Of the nine cases of malpresentation, one was a transverse lie in the late first stage of a strong labour in a multipara; the lie was easily corrected by external version, and the membranes were then ruptured to fix the head in the pelvis. Only one of the eight breech presentations was seen in the first stage; this patient was transferred to hospital, where she was safely delivered. Two of the others were complicated by prolapse of the cord, but both babies were extracted alive. One breech baby was stillborn but was known to have died before labour. Another was born alive but showed evidence of brain damage; it weighed over 13 lb. (5,900 g.). In most of the breech cases the malpresentation had not been diagnosed antenatally, but in at least three the general practitioner had undertaken to conduct a breech delivery at home, a policy with which I do not agree.

TABLE IV.—*Intra-partum Consultations (63 Cases)*

Delay in labour	39	Malpresentation	9
First stage	17	Breech	8
Second stage	14	Shoulder	1
Third stage	8	Post-partum haemorrhage	4
? Disproportion	10	Bucket-handle tear of cervix	1

Delay in First Stage

This was sometimes difficult to evaluate because it was impossible to ascertain exactly when labour had started. The cases in this group fell into three categories: the slow starters, those with true primary uterine inertia, and those with incoordinate uterine action. The slow starters were so termed because they had been a long time apparently in labour, but by the time I saw them they were having strong pains and making progress, and required no treatment other than analgesia. Two of the six in this class were indeed already in the second stage by the time I examined them.

Primary uterine inertia was considered to be present when the pains were of average or below average strength and infrequent. The slow progress of labour, as evidenced by the slow dilatation of the cervix, was therefore not unexpected. These cases were either transferred to hospital at once or treated initially at home, according to the presence or absence of other complications (such as malpresentation, malposition, doubtful disproportion), the general condition of the patient, and the length of time she was said to have been in labour. In favourable cases reassurance and mild sedation were followed at home by the active measures of enema and rupture of the membranes, reinforced in some of the earlier cases by the injection of 1 unit of oxytocin intramuscularly every half-hour to a maximum of six doses. But these measures were taken on the understanding that if they were not effective in stimulating normal uterine action in four to six hours the patient was to be sent to hospital. It was regarded as an important point in management to sustain the morale of the patient and her relatives. Three of the five women in this category were transferred to hospital, where one of them was eventually delivered by caesarean section.

Incoordinate uterine action, a form of uterine inefficiency largely confined to primigravidae, was regarded as a more serious condition, warranting the transfer of the parturient to hospital in every case. The diagnosis was made on the typical clinical picture of frequent painful contractions, which tended to be confined to the sacral region or hypogastrium, with lack of progressive dilatation of the os. The reversal of the normal time relationship between pain felt by the patient and contraction palpated by the attendant, with the pain preceding and outlasting the contraction (Jeffcoate, 1955), was a most useful diagnostic sign. In three of the six cases the foetal head was in the occipito-posterior position. Three of the women were eventually delivered abdominally.

Delay in Second Stage

This worried the general practitioner more because he regarded the foetus as being in greater jeopardy now than when the first stage was prolonged. The most common cause of delay in this group was a diminution in the strength of the contractions. In 7 of the 14 women this was the only impediment to normal progress, but the doctor forbore from applying forceps because of the traditional fear of subsequent atonic post-partum haemorrhage. It was demonstrated that such fear could be obviated by giving 0.5 mg. of ergometrine intravenously at the close of the second stage, supplemented by an equal dose given intramuscularly after delivery of the placenta. The substitution of local analgesia by pudendal block for general anaesthesia afforded a further safeguard, and several general practitioners expressed their regret that they had not previously been taught, before or after qualification, the technique of pudendal block. A recent report on general-practitioner obstetrics (College of General Practitioners, 1957) declared that there was much scope for the more frequent use of local analgesia and of "prophylactic" ergometrine in domiciliary obstetrics. The latter procedure, however, necessitates the presence of two doctors at delivery so long as midwives are forbidden to give intravenous injections.

In four cases the delay in the second stage was associated with transverse arrest of the head, while in a fifth the position was occipito-sacral. All were delivered safely outside hospital. Only 2 of the 14 patients with delay in the second stage were transferred to hospital. Both were primigravidae—one with a brow presentation and the other with a breech impacted in a hitherto undiagnosed small android pelvis. Both were delivered abdominally.

Delay in Third Stage

When the third stage was prolonged and the placenta was retained, the general practitioner asked regarding its removal, "When?" "Where?" and "Under which anaesthetic?" Following a review by Sheehan (1948) of the factors operative in fatal cases of shock in obstetrics, it has become general practice not to allow the duration of the third stage to exceed one hour; and if the placenta is to be delivered within the hour preparations must be initiated within 40 minutes of the end of the second stage.

In this series the principle was followed that if the baby was born at home the placenta was best delivered at home, for fear of shock or haemorrhage or both starting in the no-man's-land of the ambulance. This is good policy also when there is third-stage bleeding, the general condition of the patient being sustained meanwhile by infusion or transfusion by the doctor or the summoned flying-squad. General practitioners were therefore encouraged to carry among their midwifery equipment a giving set and a bottle of blood substitute.

As the anaesthetic for manual removal of the placenta in the patient's home, where there was usually a large open fire in the room of confinement, chloroform was found most useful. However, it was not used if the pregnancy had been complicated by toxaemia, or if the labour had lasted more than 24 hours, or if the drug had already been administered for the delivery. The safe use of this anaesthetic should still be taught to medical students.

Post-partum Consultations

This group (Table V) was, not unexpectedly, the smallest. Only one case of an acute depressive state was seen post partum, probably because the services of the psychiatrist were sought rather than those of the obstetrician. Three cases were seen antenatally (Table I). It was considered that a woman with a depressive state or with a history of such an episode in relation to previous child-bearing was best booked for delivery at home if there were no other contraindications to domiciliary confinement. This was because the woman was thought to be less subject to additional stresses at home than in the unfamiliar surroundings of a hospital, and because her own relatives at home would appreciate those warning minor changes of mood more quickly than would the hospital attendants who knew her less well.

TABLE V.—*Post-partum Consultations* (23 *Cases*)

Venous complications	7	Depressive state	1
Puerperal sepsis	4	Uterovaginal prolapse	1
Secondary P.P.H.	3	Rectal prolapse	1
Broken-down perineal repair	2	Anaemia	1
Breast infection	2	Vomiting	1

Venous Complications

Venous complications in the legs were the commonest indication for post-partum consultation. The questions asked by the family doctor were, in effect, "Home or hospital?" and, "Anticoagulants or not?" In answering these, a distinction was made between superficial and deep thrombosis. In the former, which usually occurred in veins previously varicose, anticoagulants were not advised and the patient was allowed to continue her lying-in period at home. In deep thrombosis, however, anticoagulants were necessary to reduce both morbidity and mortality; and as this therapy required strict laboratory control the patient was transferred to hospital.

Three cases of thrombophlebitis were seen antenatally (Table I) to which the same principles were applied. Foetal death after antenatal anticoagulant therapy has been reported in this country (Gordon and Dean, 1955), but in a series of nearly 500 similar cases treated on the Continent no untoward effect on the foetus was noted (König *et al.*, 1954).

Summary and Conclusions

Problems in general-practice obstetrics, as seen by a consultant, have been reviewed and some guidance has been offered on when the family doctor might safely continue to treat the patient outside hospital. Both consultant and general practitioner should appreciate that the latter works under at least one notable disadvantage—namely, that he is liable to pressure and agitation from the patient and her relatives to a degree against which

the hospital obstetrician is largely insulated by distance and the intervention of nursing staff. This is particularly true when pregnancy is prolonged or labour protracted.

Although a large volume of opinion in Britain favours the abolition of domiciliary midwifery, the practice is likely to continue for many more years for at least two reasons: first, many women still insist on being delivered at home; and, secondly, there are not enough hospital maternity beds to cope with all labours, especially while the parturient is expected to spend 10 days in hospital after delivery. The medical student, who is more likely to be destined for general practice than for any other branch of medicine, should therefore be taught undergraduate obstetrics in a perspective that will enable him to realize the scope and the limitations of domiciliary midwifery. This perspective should be maintained during the resident postgraduate training that he should be required to undertake before acting as a general-practitioner obstetrician. It follows that full-time university teachers of obstetrics should be allowed, and encouraged, to participate as consultants in domiciliary midwifery; otherwise the major part of the training of future general-practitioner obstetricians may be received at the hands of those who have never seen or attended a pregnant woman in her own home.

REFERENCES

Bound, J. P., Butler, N. R., and Spector, W. G. (1956). *Brit. med. J.*, **2**, 1191, 1260.
Burnett, C. W. F. (1957). *J. Obstet. Gynaec. Brit. Emp.*, **64**, 79.
College of General Practitioners (1957). An Obstetric Survey by Members and Associates of the South-West of England Faculty. *Research Newsletter*, No. 14. Suppl.
Eastman, N. J. (1956). *Williams' Obstetrics*, 11th ed., p. 423. Appleton-Century-Crofts, New York.
Gordon, R. R., and Dean, T. (1955). *Brit. med. J.*, **2**, 719.
Jeffcoate, T. N. A. (1955). In *British Obstetric and Gynaecological Practice: Obstetrics*, edited by E. Holland, p. 560. Heinemann, London.
König, F. E., Reich, T., and Steinbrüchel, M. (1954). *Schweiz. med. Wschr.*, **84**, 440.
Racker, D., Burgess, G. H., and Manly, G. (1953). *Lancet*, **2**, 953.
Sheehan, H. L. (1948). Ibid., **1**, 1.
Smith, J. A. McC., Jennison, R. F., and Langley, F. A. (1956). Ibid., **2**, 903.

INFLUENZA

REPORTS FROM GENERAL PRACTITIONERS

We are much indebted to the general practitioners whose names appear below for their reports on the outbreak of influenza.

Sudden Onset

Drs. R. J. F. H. PINSENT, L. A. PIKE, and R. H. MORGAN (Birmingham) write: The diagnosis "influenza" began to appear on case sheets in the practice during the third week in January, increasing in frequency and replacing "coryza" almost completely during the following weeks. At first young adults were affected, and cases occurred in groups in different localities, but later the load was spread evenly by districts and age groups. Of the first 300 consecutive consultations and visits by one partner in February, 92 (31%) were on account of influenza. No children under the age of 5 have been affected so far.

Symptoms.—The character of the illness differs little from that of previous epidemics. The onset is sudden, with headache, muscle pains in limbs and back, sweating—sometimes profuse—shivering, and weakness. Pyrexia of 101–102° F. (38–39° C.) may last for 48 hours. Vomiting is common, sometimes diarrhoea, and in patients thus affected the raised temperature persists longer. Vertigo, with maintained pyrexia, occurs when patients get up too soon.

Moist sounds may occur in the lungs of older patients and those known to have previously had bronchitis. The signs usually subsided with the fever, unless bacterial infection followed, with a change to purulent sputum. In about half the cases there was a boiled-ham-coloured hyperaemia of the palate and fauces, with swollen lymphoid follicles on the posterior pharyngeal wall.

The course of the disease was mild in the young adult, but debility sometimes lasted up to 10 days. Relapse has occurred in two patients so far, bronchopneumonia in three others. No patients have died to date.

Specimens for serological investigation were collected during the first week of the epidemic, but no results are yet through. One has the impression that the people seen now are those who escaped infection in the epidemic last year, though no confirmatory evidence has been sought.

Treatment.—This has been symptomatic, with sufficient rest in bed, fluids, and tinct. benz. co. steam inhalants. Tab. codein. co. has been prescribed by two partners, paracetamol by one. Impressions of clinical effectiveness will be compared. Pholcodine linctus has been used for troublesome coughs. Antibiotics have been given only when there was clear evidence of superadded bacterial infection, tetracycline being prescribed for the patients with pneumonia.

Few Cases

Dr. KEITH HODGKIN (Redcar, Yorks) writes: In Redcar so far there has been little evidence of influenza, although reports suggest that West Hartlepool, only 12 miles away, may have been hit by the epidemic 14 days ago. Since the end of the serologically proved second wave of Asian influenza in March, 1958, there has been little clinical and no serological evidence of influenza in this practice. Fourteen days ago we had an outbreak in a single household of an illness which satisfied the three main clinical criteria for influenza—high household attack rates, known fever, and cough—but there have been no further suggestive cases.*

The Table on page 502 shows that the weekly attack rates for the main respiratory diseases in this practice are about average.

My thanks are due to my partner, Dr. Philip Edmundson, who helped collect the information on which this report is based.

Short Illnesses Called "Flu"

Dr. C. A. H. WATTS (Ibstock, Leics) writes: January to March inclusive are generally accepted as being the busiest months of the year for the general practitioner. The work this season has been patchy. In rural districts, except in the rare pandemic, it is most unusual for all the villages to be affected at the same time. Thus, while one part of the practice has been very busy, other parts have been comparatively quiet for the time of the year. The measles epidemic is just beginning to crop in two widely separated areas. There have been a number of short febrile illnesses which the patients delight to call "flu," but there has been nothing like the outbreak of Asian influenza which occurred in the fall of 1957. Most of these cases are back at work in four or five days, but a few are complicated by sinusitis and otitis media.

There has been more fog in this part of the world this season than for many years, but it has never become smog. The winter has been colder and more sunless than usual, and the old folk have suffered in consequence. There has been some bronchopneumonia among them and among the chronic bronchitics, but with antibiotic treatment these illnesses have been well controlled. One death from bronchopneumonia occurred in an aged person in early February, but that has been the only chest fatality in the practice during the entire twelve-month period. Indeed, considering the weather the patients liable to chest disease have fared rather better than one would have expected.

Among children there have been some cases of acute chest disease and wheezy bronchitis. A few have had a very trying and persistent cough for many weeks. It is possible

*STOP PRESS.—Laboratory examination shows that this family had influenza A (Asian). The only member not to succumb was a girl who had influenza during the epidemic last year, when the others escaped it.

Respiratory Diseases at Redcar, Weekly Attack Rates per 1,000 N.H.S. Patients in Practice

	Influenza* (Rate per 1,000)			Acute Bronchitis† (Rate per 1,000)			Coughs (Rate per 1,000)			Acute Exudative Tonsillitis (Rate per 1,000)			Acute Laryngitis and Tracheitis (Rate per 1,000)		
	1957	1958	1959	1957	1958	1959	1957	1958	1959	1957	1958	1959	1957	1958	1959
Jan. 1–7 ..	0	0·4	0	6·7	5·7	3·5	9·7	6·1	1·2	0·5	1·1	0·6	0·9	1·5	0·3
.. 8–14 ..	0	2·3 (3)	0	1·3	3·5	3·5	1·8	6·5	1·8	1·3	2·3	2·1	0·5	0·4	0·3
.. 15–21 ..	0	5·0 (5)	0	4·4	3·8	2·8	4·9	2·3	2·4	1·8	0·4	1·2	2·7	0	0·3
.. 22–28 ..	0	9·9 (3)	0	5·8	4·2	3·1	3·5	2·3	2·1	1·8	1·9	1·8	1·3	0·8	0·9
.. 29–Feb. 4	0	13·7 (5)	0·6	8·4	4·6	3·1	6·2	3·1	4·6	0·5	3·4	1·8	2·7	0·4	0
Feb. 5–12 ..	0	5·7 (2)	0·6	3·5	1·5	5·7	4·0	2·3	5·2	3·1	2·3	3·4	1·3	0·8	0·6

* Numbers of serologically proved influenza cases shown in parentheses.
† Acute bronchitis—all cases of cough with either fever or moist adventitious sounds in the chest.
Colds are not recorded in this table as it is considered that the numbers reported to the doctor bear little relation to their prevalence.

that some of these cases may well have been a mild whooping-cough or the disease modified by immunization. It is clear that, as the prophylaxis against pertussis increases, it is becoming more difficult to recognize the disease.

To summarize, I would suggest that respiratory infections this year have not been either prevalent or severe in this area, and those which have occurred have made a good response to one or other antibiotic.

Influenza Myringitis

Dr. F. H. STAINES (Callington, Cornwall) writes: The current picture of respiratory diseases in this practice is seasonal (though a little above the average), and not as yet epidemic. "Problem cases" have been few, and no bacteriological or virological investigations have proved necessary. Weather has been mainly dry, with average temperatures. There has been some hill-fog (i.e., cloud) but no smog.

BACKGROUND INFORMATION

Bronchitis.—This practice has, judged by the criteria of "not more than two short chest illnesses in a year with normal chest health between," a low incidence of "chronic bronchitis." Last year this was calculated as 1 in 700, excluding known asthmatics and bronchiectatics. The figures given below of current "bronchitis" are therefore high.

Tonsillitis.—Peak incidence here occurs in June and December. Last year, from August through the autumn, about 50 cases of tonsillitis were seen, of notable chronicity and with little constitutional upset, but with persistent and recurrent "orange-pip" concretions in the tonsillar crypts. These numbers I have not seen in former years. All of the four cases swabbed grew penicillin-sensitive *Streptococcus pyogenes*. One of these patients suffered a troublesome and persistent spasmodic reflex vasodilatation of the auricle, cheek, and upper neck; another has had recurrent descending chest infection. Is it possible that a similar sort of infection may have been responsible for many tonsillectomies in the "focal sepsis" era?

Influenza.—A small number of sporadic cases have been diagnosed as influenza since early January. Symptoms have been lassitude, sore throat, cough, and substernal pain or oppression. Signs have included low-grade pyrexia, pharyngitis, and tachycardia—the latter in many of the cases persisting at rates between 100 and 150 per minute, for 10 to 15 days. None have suffered chest infections, but myringitis has complicated 1 case in 3.

PRESENT INFORMATION

I regret that no figures are available of surgery attendances for respiratory disease. The number of "new calls" to visit patients suffering from respiratory diseases in the period January 14 to February 13 are appended, and show some interesting features.

Bronchitis (Including One Case of Bronchopneumonia).—There were 15 patients, and they included two of the known "chronic bronchitics" of the practice and three previously healthy young adults. In 2 of the 15, abnormal moist sounds in the lungs persisted beyond 10 days; and in one, beyond 20 days.

Upper Respiratory-tract Infections (Including Tonsillitis, Sinusitis, Nasopharyngitis, Severe Coryzas, and Acute Otitis Media).—There were 48 patients. In one catarrhal family of three small girls there were five separate attacks of acute otitis media (of 10 cases in the practice during the period specified). Only one case of tonsillitis (of the 15 seen) was of the sort described above as seen here last autumn, but there were three typical cases of scarlet fever. One of the three cases of sinusitis was markedly similar to, though of shorter duration than, the severe case treated during the Asian influenza of October, 1957.

Influenza.—The 17 cases have in the main followed the features described above. However, two patients suffered lassitude, cough, and low-grade pyrexia for nearly a week without the discovery during examination of any physical signs, until a typical influenzal myringitis finally appeared. In three other patients similar tympanic appearances were found at the first examination. All have completely resolved spontaneously.

Increase in Otitis Media

Dr. R. E. HOPE SIMPSON (Cirencester, Glos) writes: The influenza epidemic is probably just starting in this area as it appears to have done in other parts of the country. The weekly attendances for clinical influenza in a general practice of about 4,000 patients from the beginning of the year have been as follows: 7, 5, 4, 5, 6, 10. But in the last week-end more cases were seen than in the previous six weeks.

Of five residential schools, only two report an outbreak. One of them, a girls' school with some 250 pupils, had 30 cases between February 1 and 11 and have had none since. The second, with 54 pupils, has had fewer than 20 cases. The latter school states that the disease is easily distinguishable from the seasonal colds because it is characterized by backache, aching in the knees, and vomiting as well as cough, and that many of the children complained of profound lethargy for several days before the onset of the disease. The day schools report no unusual prevalence.

One can sum up by saying that the present season has so far been singularly free of influenza, and we must expect the epidemic to appear at any moment. During the last few days there has been an increased prevalence of cases of otitis media in children. It may be that this reflects the onset of mild influenza.

Two Infections

Dr. G. I. WATSON (Peaslake, Surrey) writes: On January 20 a typical case of influenza was recognized, but in the previous week six cases of acute respiratory infection were seen in three families and diagnosed as acute bronchitis, laryngitis, or sinusitis. In the month from January 13 I have attended 96 people in 63 families suffering from acute respiratory disease; of these, 85 people in 55 families probably or certainly had influenza. In 37 of the affected families, in which the first patient was an adult or teenager, 35 (95%) did not have Asian influenza during the 1957–8 epidemic, suggesting that many of them are now being infected with that strain of virus-A influenza.

On the other hand, in four local boarding-schools an influenza-like illness has affected a high proportion of pupils. At one of these, virus-B influenza has been confirmed serologically, and at another at least three boys had proved Asian influenza in 1957, which suggests that this illness may also be virus-B influenza. Five local day schools

are now similarly infected, so it appears that two types of influenza are prevalent, but only virus B seems to be spreading locally. One boy appears to have had an attack of each, the first caught in London (probably virus A) and the second caught at school (probably virus B).

The secondary attack rate in 19 previously uninfected families in which the primary case took ill more than a week before writing was 39/64, or 61%. This is about the same as the highest infection rates encountered during the 1957 epidemic. At least six families, comprising 17 people, have been totally infected, and in several others more than half the family has succumbed. On the other hand, as in 1957, several teenagers with rooms of their own have not infected the rest of their families.

Symptomatology.—This varies with age, aching being an adult symptom rarely mentioned or admitted by those under puberty. Headache, aggravated in adults by coughing, is the predominant symptom, but often lessens, without drug treatment, after the peak of fever. Cough increases in frequency after the first few days and is almost universal during convalescence; in 1957 such patients spread influenza to twice as many people as did those who had no cough (unpublished observations). Coughing is painful only when present during the acute stage; many complain of persistent pain in the throat, not aggravated by swallowing, and they have no tenderness of the tonsillar glands. Fever rising to 103° F. (39.4° C.) is common, and the peak may not be reached till the second day; thus several patients keep going during the day of onset. The biphasic pattern has occurred in about one out of every four or five records. Several patients have had fever for five days; but one child in a family of five (all affected) was only febrile for less than 12 hours. Reddening of the conjunctivae has been almost universal, and in children may be the only evidence at onset, apart from fever. Neither vomiting nor profuse sweating has been seen except in patients who were taking antipyretics; nor has convalescence been prolonged by prostration or depression.

Treatment.—Warm, moist air in the bedroom, plenty to drink, and a sufficient dose of butobarbitone or glutethamide at night and occasionally in the afternoon: these are my principal aids. Mist. salina *B.N.F.* is given freely during fever, but antipyretics are not dispensed except to a few patients who cannot retire to bed—usually the woman of the house—and I advise against their use unless headache prevents sleep in spite of the hypnotic.

Complications.—There have been no deaths. Out of the first 85 patients with probable influenza, nine adults and two children (14%) have shown abnormal signs in the lungs, often on the second day of illness. One adult also developed auricular fibrillation. In view of past and recent failures with penicillin alone, the drugs used have been chloramphenicol four times, oxytetracycline four times, penicillin and streptomycin together twice, and penicillin alone once—and in every case with good results. Tender sinusitis and undue laryngitis have each occurred in four patients (5%), while one had both conditions. Each has responded quickly to penicillin orally or by injection. The remaining 65 patients (76%) have recovered without complications. One other patient who succumbed to an attack of classical left lobar pneumonia has not been included in the series, as none of three family contacts have taken ill since.

Widespread Among Young Adults

Dr. JOHN FRY (Beckenham, Kent) writes: In spite of press reports suggesting a mild and localized epidemic, the recent outbreak of influenza has been extremely widespread and extensive, causing tremendous loss of time from school and work, and causing a very great deal of work to the family doctors in this area. In this practice the volume of work in the past two or three weeks has been trebled.

The first cases of real influenza began to appear around January 17–19, but the peak has been in the past week February 7–14, and the epidemic still goes on apace with some 30 new cases each day. In numbers it has been as extensive as the "Asian flu" of 1957, and so far approximately 400 patients have been seen suffering from influenza in this practice of 5,000, while as many, probably more, have treated themselves without seeking medical attention.

Like the 1957 epidemic the onslaught of the virus has been principally on the younger members of the community, between 10 and 40 years of age. It has been children in the secondary and grammar schools who have suffered most. Although there have been a few sporadic cases in the elderly, most have escaped. Influenza has occurred in young children, but the impression has been that the incidence at this period has been less than in the teenagers.

Symptoms.—The clinical features have been classical. A sudden onset, the patient usually being able to recall the exact hour and minute of onset of symptoms. Shivering and extreme malaise have been followed by marked bodily aching, drenching sweats, aching eyes, stuffy nose, and a dry irritating cough. Nose-bleeds have been quite frequent in the teenagers and children. The signs, too, have been characteristic. After the first few cases one could walk into the sick room and diagnose the case from the end of the bed. The patients all looked most miserable and dejected, the eyes were suffused, there was the cough, and the whole body was warm and clammy. The fauces were not excessively red, and in uncomplicated cases no abnormal signs were found in the chest or ears.

Complications.—Mild or moderate chest complications have occurred in 21 patients so far—a rate of 5%. None has required admission to hospital. These chest infections have been bronchitic or pneumonic. The latter have been mainly mild segmental pneumonias characterized by localized areas of moist sounds at one or other base. During this same period there have occurred 40 cases of acute otitis media in children, but in only a few could they be attributed to a preceding attack of influenza.

Treatment.—The management of these great numbers of patients has been essentially empirical and largely symptomatic, the acute phase being treated with aspirins and linctus, with rest in bed for 2–4 days. This acute phase seemed to last for 3–6 days and was often followed by marked debility for a further week. Men at work required 10–14 days' sick leave. Complications were treated with intramuscular penicillin in the first instance, and the broad-spectrum antibiotics were necessary on only one occasion.

Compared with previous epidemics of influenza in this practice this has been (and still is) extremely widespread, but with a relatively low rate of complications. Clinically it is very much like the influenza-A epidemic of 1957, but the results of serological tests are not yet available, so the causal strain of virus is not yet labelled. However, it is of interest that only 20 victims of the present epidemic suffered from "Asian flu" in 1957.

Dr. G. E. H. Callebaut has worked with me during this epidemic and my sincere thanks are due to him.

Spread in a Hospital

Dr. R. M. MCGREGOR (Hawick, Roxburghshire) writes: In this area January was a month of cold weather, with the fields and the roads covered by a layer of frozen snow. During the second week a perceptible rise in the sick rate occurred, but this soon subsided. On January 30, however, a thaw set in, and coincidental with the milder weather the number of sick rose steeply. This rise has continued and it is probable that the peak has not yet been reached.

With a number of patients it is difficult to elicit any physical signs to account for the discomfort about which they complain. Others show a marked injection of the fauces with only a minimum of pyrexia. The majority, however, have a fever for one or two days and complain of generalized aches and pains. This group usually show considerable upper respiratory irritation with headaches only occasionally. No age group is predominantly affected, but so far the very young have escaped.

(*Continued at foot of next page*)

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Influenza Virus Polyvalent Vaccine (Pfizer).—This is a similar type of vaccine to those described in this column on December 6, 1958 (p. 1410), except that it contains no mineral carrier. The final vaccine contains merthiolate 0.1 mg. per ml. as a preservative. The virus strains included are 2 parts of Asian A, 1 part each of two other A strains, and a B strain, 1 part. As recommended earlier, such vaccines are best given in 1-ml. doses, deeply subcutaneously, and should not be given to persons sensitive to egg protein. Children need smaller doses. Though polyvalent vaccines are much used in the U.S.A., many workers in Great Britain believe that a monovalent Asian, or at most a bivalent one, may be preferable at the present time. The immunity induced by influenza vaccines reduces the number of cases of influenza to about one-third of the number found in the non-inoculated, and is unlikely to last for more than one winter.

N.H.S. basic price: multi-dose 5-ml. phial, 37s. 6d.

Injection of nikethamide *B.P.*
Anacardone (British Drug Houses).
Coramine (Ciba).
Corediol (Richter).
Corvotone (Boots).

Nikethamide, or nicotinic acid diethylamide, is a stimulant to the respiratory and cough centres and exerts this effect in doses which have little action on other portions of the central nervous system. It has no important direct effects on the heart or blood vessels, and its use as a cardiovascular stimulant is irrational. Though its effect on the respiratory centre is dramatic, this action is exceedingly evanescent. It is of value in counteracting the excessive depression of the centre by volatile anaesthetics, and for patients seriously ill with pneumonia or bronchitis. It is ineffective when given orally and should always be administered intravenously, for which it is supplied in ampoules. The range of dose ordinarily administered is 0.25 to 1 g.

N.H.S. basic price:—six 2-ml. ampoules: injection of nikethamide *B.P.*, 2s. 6d.; anacardone, 2s. 6d.; coramine, 3s.; corediol, 2s. 6d.; corvotone, 2s. 6d. Ampoules of other quantities also available.

(Continued from preceding page)

Attention was first attracted to this infection by some cases of raised temperature among the inmates of a hospital for the elderly sick which is at present under the care of this practice. Here the disadvantage of hospitalization was made manifest by the speed with which this infection spread throughout the whole hospital of some 40 beds. Those patients who had a pre-existing chronic bronchitis suffered severely, and the results were doleful for those whose myocardium was not capable of accepting further strain.

The spread of the infection throughout the community at large was slower but has now become extensive. Among schoolchildren and young adults no severe complications have been encountered, though it is noticeable that where a husband and wife or two children occupy the same bed each appears to infect the other. If 24 hours or more has separated the onset of symptoms, the one that was showing signs of recovery becomes pyrexial once more, and this second infection has always proved more troublesome than the first.

Treatment.—The policy followed in this practice is to give to those who show severe injection of the fauces 1,200,000 units of a mixed penicillin. All other pyrexial cases are given sulphadimidine. It is thought that the sulphonamide drug is of more value than constipating cough mixtures and is less irritative to the mucus membrane of an empty stomach than aspirin.

Correspondence

Immunization Programmes

SIR,—The medical officers of health of certain metropolitan boroughs (*Journal*, February 7, p. 362) want the views of others. They can have ours. Their programme is impracticable. It involves ten injections before the child is 2. How many parents will complete a programme of ten? The many defaulters will leave a dangerously high percentage of children unprotected against diphtheria and tetanus.

Their programme will also leave many children frightened of doctors. We find the intelligent, sensitive child remembers pricks given after 9 or 10 months of age. He is resentful or frightened because he is too young to understand the doctor's attack on his person. Thus the G.P. is unable to diagnose the early appendix because the child is crying and rigid.

We are sure the risks of contracting polio following combined diphtheria-pertussis-tetanus protection are less than the risks of leaving many children unprotected from diphtheria or many frightened of the doctor who should be a friend.

We combine vaccination with the post-natal visit at 6 weeks. Triple antigen is given from 3 to 7 months (except in polio epidemic periods). The first two polio injections can then be given from 7 to 9 months. Among patients for whom we do both maternity work and infant welfare we can boast a much higher percentage of completely protected children than public statistics show for the population at large.—We are, etc.,

JOAN WAGSTAFF.
HELEN WAGSTAFF.

London, E.4.

SIR,—It is gratifying to see from the letter of Dr. E. C. H. Huddy (*Journal*, January 31, p. 303), and from that of Dr. M. Adams and his colleagues (*Journal*, February 7, p. 362), that so many experienced brains are at work on this important matter. There is one thing that has to be borne in mind in assessing the merits of the various procedures suggested, and that is that knowledge of some of the finer points of immunization is still accumulating, and elucidation of certain problems may cause us to modify our ideas as to what can safely be undertaken in infancy and what cannot.

One disturbing feature about the routine suggested in both letters is the placing of diphtheria prophylaxis in a subsidiary position, just because the disease is not with us now. Only because so many parents dread whooping-cough do some of them accept diphtheria immunization also, in the form of a combined diphtheria-pertussis prophylactic, when bringing their children to clinics. Again, one feels that, with the multiplicity of injections involved, many will fall by the way, with the result that one or more of the treatments would be incomplete and not fully effectual.

Just because the incidence of diphtheria is minute at the moment, who can tell when it may return in full force, as it has done in the past? If we adopted any routine which resulted, in a few years' time, in a material reduction in our immunized rate, the door would be wide open to imported infection. Many of us will remember what a ghastly scourge diphtheria was in the early years of the century: dare we risk a recurrence of that?

One would very much like to know how many cases of associated post-injection poliomyelitic paralysis have been recorded in babies inoculated at 2, 3, 4, or 5 months with three injections of diphtheria-pertussis prophylactic without mineral carrier. Quite large numbers of tiny infants have now received this treatment, often throughout the year, and if any cases have been recorded it is important that we should know of them and also at precisely what age the inoculations were commenced. I concluded[1] that the risk of poliomyelitis under the age of 6 months was at its lowest, and advocated very early immunization as a possible measure of safety. Statistically my own freedom from paralytic trouble over the last eight years or so may be of no value, but, added to the experience of others, it might amount to something. I have given enormous numbers of combined diphtheria-pertussis injections, throughout the year, during the last seven years.

It seems certain that preventive medicine will stand or fall in the future solely on the question of whether suitable multiple antigens, free from danger, can be evolved: these will have to be designed so as to attempt neither too much nor too little at a time. The danger of overloading the immunity mechanism of the body is quite a real one. Until certain matters of vital importance are elucidated, I should hesitate to endorse or decry the procedures suggested by either of your correspondents, with the exception of expressing concern at any step which might result in the lowering of our herd immunity to diphtheria. Some of your correspondents will know that there is to be a symposium on immunization at the Wellcome Foundation commencing on May 4 next. It might be well to postpone any positive action until the conclusions of this conference have been arrived at.—I am, etc.,

Broadbridge Heath, Sussex. GUY BOUSFIELD.

REFERENCE

[1] Bousfield, G., *Lancet*, 1951, **1**, 1028.

SIR,—Believing that the family doctor should play his part in the immunization programme, I am disturbed that the child's introduction to his doctor should be such a long series of injections as is outlined in the letter from the medical officers of health of some Metropolitan boroughs (*Journal*, February 7, p. 362).

Pertussis immunization being less certain in effect than the others mentioned, might we not vaccinate against smallpox at 3 months; immunize against poliomyelitis at 6, 7, and 14 months; and then, having the courage of our convictions and disregarding present official advice, assume adequate immunity to poliomyelitis and give triple antigen (diphtheria, pertussis, tetanus) by three injections in the second year? B.C.G. vaccination would be done as suggested at the age of 13.—I am, etc.,

Shrewsbury. JOHN B. LONGMORE.

SIR,—We commend the efforts of our London colleagues (*Journal*, February 7, p. 362) to formulate an agreed immunization programme. Their programme, with the exception of one item, takes into consideration the ages at which there is greatest risk of morbidity and mortality and the age at which the various procedures are most efficacious. The exception we have in mind is vaccination against smallpox. We would not recommend it during the first month of life because there is a higher failure rate in the neonate; when successful the lesion is not always as small and neat as in older infants. We like to see infants well established in good feeding habits and gaining in weight before offering any immunizing procedure. Hence we suggest that vaccination against smallpox be inserted in the programme at 8 months of age after the second poliomyelitis inoculation.

Without doubt the length of the programme will be criticized; it requires eleven visits to the doctor in the first two years of life. If the combination of antigens is the solution to this problem, the most useful combination would be a poliomyelitis-diphtheria-tetanus one. This combined antigen would be given at 6 and 7 months of age with booster inoculations at 14 months and 5 years of age.—We are, etc., W. J. MCLEOD.

Health Department, Belfast. S. N. DONALDSON.

SIR, — May I use your space to criticize the authoritative letter from the medical officers of health of Metropolitan boroughs (*Journal*, February 7, p. 362) on the following grounds?

(1) The number of procedures: 10 in the first two years. Each procedure carries its own small risk; and, the more there are, the more time and money is spent and the more likelihood of defaulters. (2) I have read that the antibody response is not fully developed until about 3 months. If this is so, then it is not worth starting the programme until then. (3) The rigid programme beloved by the administrator will never be worked through in orderly fashion. Mother and father may have to be persuaded to allow the baby to start; they may agree to one and not to others; they will certainly prefer British to Salk poliomyelitis vaccine; epidemics will crop up; appointments will be forgotten; and finally the baby will have reached a state of awareness and the mother will balk at dragging the child screaming to surgery or clinic.

I conclude that the programme will have to be tailored to the individual infant; that the advice of the Central Health Services Council should be rejected; and that the combined diphtheria, pertussis and tetanus vaccine should be used. This vaccine produces a good degree of immunity, complications are uncommon, and it saves three injections.—I am, etc.,

Harwich. BENEDICT L. HOSKYNS.

SIR,—The letter from several medical officers of health of Metropolitan boroughs (*Journal*, February 7, p. 362) on the best ages for immunization in babies is most interesting and tackles a subject where there should if possible be some uniformity of procedure. My only doubt is with their recommendation to vaccinate against smallpox in the first month of life. It appears from the accompanying Table that complications following vaccination are lowest in the second year of life.

Figures for Complications of Primary Vaccinations in England and Wales During 1950–53 Inclusive[1]

Age	No. of Primary Vaccinations	Deaths	Deaths per 100,000 Vaccinations	Cases of Non-fatal Encephalomyelitis	Rate per 100,000
Under 1 year	810,799	9	1·11	7	0·86
1–4 years ..	233,182	—	—	1	0·43
5–14 ..	175,195	—	—	4	2·28
15 years and over ..	261,217	2	0·86	6	2·30
Total ..	1,480,393	11	0·74	18	1·22

For this reason I feel it would be wisest to vaccinate at about 18 months.—I am, etc.,

Health Department, Barking, Essex. VIOLET SPILLER.

REFERENCE

[1] *Reports of the Chief Medical Officer of the Ministry of Health*, 1950–53.

Television Angina

SIR,—As society evolves (or, at any rate, changes), old dogs may sometimes have to learn new tricks. Angina pectoris, having for many years led an undisturbed existence, has been driven by the advance of mechanization away from its old haunts in the open air. Happily our new society, having done so much to obviate physical activity, has provided new occasions for the stimulation of cardiac output; and thus angina, compelled to seek a new abode, has discovered around the television set a dwelling swept and garnished.

At our clinic for patients with coronary diseases, the incidence of television angina is both high and rising. This is now, indeed, the most frequent type of emotionally provoked attack; and it may afflict those whose angina of effort permits walks of half a mile (0.8 km.) at a stretch. It affects about one-fifth of our anginal subjects. Among those who are liable to emotionally provoked attacks, only two can enjoy their television in comfort; and in some this is the only type of rest pain.

Those of your readers who aspire to mental detachment, even at the height of the chase in the "Western," may care to ponder that some hundreds of their less fortunate fellows are at that very moment clutching their chests with one hand while feeling for trinitrin with the other. It is the cowboys and their assailants who most often provoke this kind of suffering; but each man to his taste. The "Westerns" leave our Welsh patient unmoved, but for him "the sad programmes" are doubly sad. The old 8th Army man finds that Montgomery gives him a pain (in the chest—the neck, in this case, is spared). Yet even in this crisis the old soldier keeps a clear and practical mind: he leaves the room when the pain gets too bad. All our other sufferers remain at their posts. Such is the power of the tube! And for the encouragement of the advertising industry, I may add that "commercials" are entirely painless.—I am, etc.,

St. Mary's Hospital, London, W.2. G. A. ROSE.

Cardiac Pain

SIR,—As a rider to Dr. William Evans's inspiring address (*Journal*, January 31, p. 249), may I protest against patients with "heart trouble" having a salt-free diet inflicted upon them unless there be some unequivocal indication.

These unhappy individuals are reminded three times a day at mealtimes that they have a "serious heart condition." They do not enjoy their food as much as they might, and sooner or later most of them abandon the regime (dual cooking is a strain in any household)—some with guilt feelings and the half-expectation that something will go wrong, and that if it does their physician will emit an exasperated, "What did I tell you?" It is wellnigh impossible for them to cease being patients and to put their illness in the past where it belongs.—I am, etc.,

Mundesley Hospital, Norfolk. GEORGE DAY.

Tobacco Smoke

SIR,—The statistical studies of Hammond[1] in the U.S.A. and of Dr. R. Doll and his colleagues (*Journal*, February 7, p. 322) in Great Britain lead to the conclusion that the difference in average length of discarded cigarette ends may be related to the well-established difference in the incidence of lung cancer in the two countries. Indeed, the latter authors suggest that "quite a small difference in butt length might therefore result in a substantial difference in the amount of carcinogen inspired." This supposition has been fully confirmed in my laboratory by recent analytical studies upon the amounts of various polycyclic aromatic hydrocarbons in cigarette smoke.

Cigarettes of a popular brand in use in Great Britain were smoked mechanically to two different stub lengths, 15 mm. and 35 mm. The choice of length was made because an early survey of average stub length in England[2] gave the shorter length and because the longer length represents the consumption of half of the regular-size (70 mm.) cigarette. It happens that this latter stub length is the most common in U.S.A. The analytical procedures for collecting the smoke and determining hydrocarbons in it were as described elsewhere.[3,4] In the Table are shown the amounts in micrograms of a number of hydrocarbons found in the smoke from 100 cigarettes.

Hydrocarbon	Smoke		Stub Extract	
	15 mm.	35 mm.	15 mm.	35 mm.
Acenaphthylene	16·0	8·5	3·8	8·0
Anthracene	22·0	23·0	12·0	42·0
Pyrene	15·0	7·1	5·3	17·0
Fluoranthene	10·0	8·0	36·0	12·0
1:2-Benzanthracene ..	14·0	8·0	8·5	14·0
3:4-Benzpyrene	3·0	0·7	2·0	3·0
Anthanthrene	0·3	0·6	0·3	0·7
Coronene	1·1	0·5	11·0	0·4

Some important comments should be made on these results. Of the two carcinogenic hydrocarbons 1:2-benzanthracene and 3:4-benzpyrene, the latter has been shown to be more active than the former. Considered together the amounts of these compounds inspired are reduced by one-half when long stubs are discarded, but 3:4-benzpyrene amounts are reduced to less than one-quarter. In the third and fourth columns of the Table are shown the amounts of the various hydrocarbons found in the residual stubs. Here it will be seen that the stubs are capable of retaining considerable quantities of the hydrocarbons and also that, as the smoking process proceeds, they tend to collect larger amounts of the compounds of heavier molecular weight. It also appears that the compounds of lighter molecular weight are more subject to destruction during the repetitive distillation that is part of the very complex series of processes occurring during smoking.—I am, etc.,

Department of Chemistry, Sir John Cass College, London, E.C.3. ARTHUR J. LINDSEY.

REFERENCES

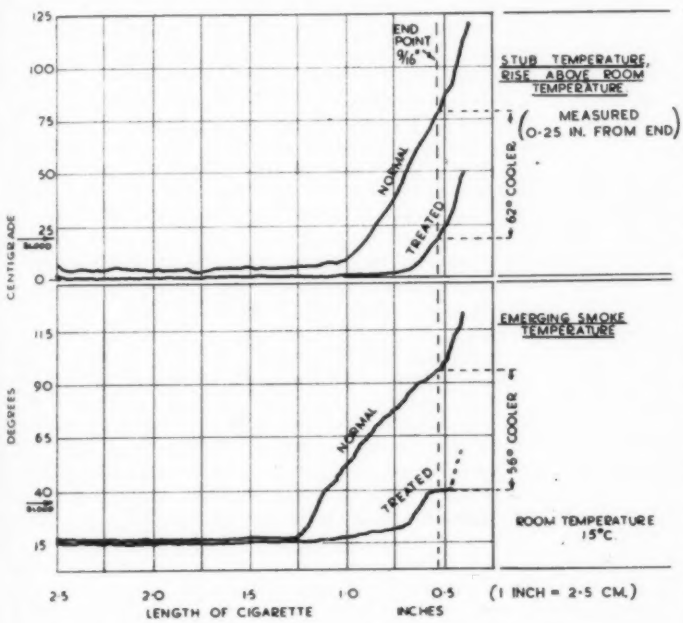
1. Hammond, E. C., *Brit. med. J.*, 1958, **2**, 649.
2. Commins, B. T., Cooper, R. L., and Lindsey, A. J., *Brit. J. Cancer*, 1954, **8**, 296.
3. Cooper, R. L., and Lindsey, A. J., ibid., 1955, **9**, 304.
4. Lindsey, A. J., *Anal. chim. Acta*, 1959, **20**, 175.

SIR,—The three extremely interesting papers on tobacco-smoking you present in your issue for February 7 (pp. 317, 322, and 325) persuade me to bring to your attention the conclusions of some measurements on the physics of cigarette-smoking. Observations were made with recording pyrometers and air-flow gauges, coupled with measurements of the oxygen concentration in the inhaled smoke and

colorimetric estimations of the total tar extraction in water–acetone mixtures.

Cigarette paper is porous to air, and the amount of air passing through the paper of a full-length lighted cigarette is about equal to that drawn past the burning tip. As the cigarette shortens, the paper becomes a less and less effective bypass, and for a given "draw" the concentration and temperature of the inhaled smoke increases.

The unsmoked part of the cigarette is a filter, and the extent of condensation occurring in it depends upon the temperature of the smoke–air mixture passing through. As it becomes shorter it becomes less efficient, but the importance of the observation lies in the fact that the condensate is successively reheated and redistilled as the burning tip advances. Accordingly Fig. 7 in the article by Dr. Ernst L. Wynder (*Journal*, February 7, p. 317) may be misleading, for the tar in the cigarette is not heated for only one minute as the cinder passes a given point, but—



some of it at any rate—is volatilized again and again and may receive, in all, 15 minutes' heat treatment. It is during the last third of a cigarette that the bulk of the smoke and tar is passed into the mouth. When the burning point of certain rolled-paper filter-tipped cigarettes reaches the filter, the air passing through the filter is hot enough to partially clean the filter by re-evaporating the condensate into the mouth.

A method of reducing considerably the total tar inhaled is to provide a constant level of ventilation near the stub in the form of small holes or a band of more porous paper. The changes in stub temperature and emergent smoke temperature, which follow smoke concentration closely, are shown in the accompanying Figure for average English cigarettes and for cigarettes with two needle pricks, 0.025 inch (0.64 mm.) in diameter, placed half an inch (12.7 mm.) from the mouth end. This modification can reduce the total tar extraction by 60% when cigarettes are smoked to a stub length of 15 mm. (9/16 inch).

Added air inlets near the stub reduce the power of each draw to brighten the burning point, and, as far as colour is a fair indication of peak temperatures, make a significant temperature reduction. It would seem that attention to the physics of this problem might be helpful to persons troubled with the lesser infirmities attributed to smoking, even to providing a reduction in the number of premature births,[1] and time would show whether the change in tar quantity or quality would bring the dose below the threshold for carcinogenesis.

—I am, etc.,

C. N. SMYTH.

University College Hospital Medical School, London, W.C.1.

REFERENCE

[1] Simpson, W. J., *Amer. J. Obstet. Gynec.*, 1957, **73**, 808.

Mortality from Tobacco

SIR,—Tobacco's responsibility for a proportion of cases of lung cancer and bronchitis has been further confirmed by the evidence published in your issue of February 7 (from Dr. E. L. Wynder, p. 317; Dr. R. Doll *et al.*, p. 322; and Dr. I. T. T. Higgins, p. 325). Tobacco has also been shown to be an important factor in causing the reactivation of pulmonary tuberculosis in patients past middle age.[1] As I see many patients with these three diseases, I am frequently involved in discussions on the nature and extent of tobacco's responsibility for them. I was recently told that road accidents probably cause far more deaths than tobacco, so I calculated the approximate size of the threat to life which tobacco constitutes, if the cause and effect hypothesis be accepted.

The number of deaths from these diseases is given in the Registrar-General's *Statistical Review*, and the proportion likely to be due to tobacco has been calculated by Edwards[2] from a number of published papers (see Table below).

Even this large figure of 23,000 is unlikely to include all the deaths for which tobacco is responsible, as there is less definite evidence that tobacco is a factor in producing coronary thrombosis (76,000 deaths in 1957), cancer of the mouth, pharynx, and larynx (2,800 deaths), cancer of the bladder (2,900 deaths), and peptic ulcer (5,200 deaths). Thus it seems reasonably certain that the figure of 23,000 is a conservative estimate of the deaths attributable to tobacco in 1957. This is nearly five times the figure for road accident deaths, which was 4,827.

If this is the approximate size of the threat to life, our present efforts to meet it appear ludicrous. Surely any

Tobacco Deaths in 1957

Disease (with International Classification Numbers)	Sex	Total Deaths 1957	Proportion of Deaths Probably Due to Tobacco (Edwards, 1957)	Deaths Due to Tobacco
Lung cancer (162–163)	M	16,430	84%	13,801
	F	2,689	34%	914
Pulmonary tuberculosis (002)	M	2,899	60%	1,739
	F	1,085	25%	271
Bronchitis (500–502)	M	18,962	*	6,321
	F	7,973		
			Total	23,046

* The data do not yet justify a quantitative estimation of the proportion of bronchitis deaths due to tobacco, but Edwards concludes that the majority are so caused. In view of the uncertainty I have taken one-third of the *male* deaths as a conservative figure.

community which values its health must take at least four measures to reduce tobacco consumption—namely, (*a*) a ban on cigarette advertisement, (*b*) a level of tax on cigarettes which materially lowers consumption, (*c*) control of smoking in all public places in which smokers cannot be separated (for example, cinemas, restaurants, single-decker buses), and (*d*) a really effective campaign to warn the public.

Although it is a year and a half since the Minister of Health laid on local authorities the responsibility for such a campaign, I see no evidence yet to make me think that anything is being done which is likely to change the habits of the nation. If the Ministry really wants to reduce tobacco-diseases it will have to use all its weapons and use them as if it intended to slay a very firmly entrenched opponent.—I am, etc.,

J. DONALD BALL.

Miners' Chest Diseases Treatment Centre,
Llandough Hospital,
Glamorgan.

REFERENCE

[1] Lowe, C. R., *Brit. med. J.*, 1956, **2**, 1081.
[2] Edwards, J. H., *Brit. J. prev. soc. Med.*, 1957, **11**, 10.

Onset Enuresis

SIR,—May we reply to the points raised by Drs. Kenneth and Frances Ulyatt (*Journal*, December 27, p. 1596)? We should very much like to know the incidence of onset enuresis in non-rehoused communities, but so far the only information we have is in the study of Dr. Bertil Hallgren, to which Dr. Hilda Lewis very kindly drew our attention (*Journal*, December 6, p. 1414). Our findings did not relate onset enuresis to raising the poor above their station, but showed associations which we believe were the result of sociological factors manifest in rehoused communities.

With regard to Table III in our article (*Journal*, November 22, p. 1266), it is irrelevant to our argument whether the figures were quantitatively accurate, as there is no reason to believe that the accuracy of a mother's memory is related to the number of her children. In fact, assuming that the bed-drying habits of the population have remained unchanged during the past twenty years, an analysis of our figures show that, when thinking back, mothers gave the age of bed-drying of their children on the average about three months earlier than was actually the case.—We are, etc.,

J. D. PAULETT.
E. TUCKMAN.

St. Mary's Cray, Kent.

Respiratory Failure in Bronchitics

SIR,—We read with great interest the excellent article by the late Dr. E. K. Westlake and Dr. E. J. M. Campbell (*Journal*, January 31, p. 274) and the comprehensive annotation (p. 289). However, we would like to make a few observations on the treatment of respiratory failure, since we have had quite considerable experience in this field.

For all practical purposes it is a chest infection which, in the emphysematous patient, initiates the trend of events leading to respiratory failure. Any chest infection, therefore, must be treated early and adequately. It is often missed because the patient's temperature is normal, but early indications of an infection are increasing dyspnoea and a rise in the pulse rate (headaches, drowsiness, and mental change are late features). Such a patient must be given an antibiotic in adequate dosage and for a sufficient period of time—*cost must not be a determining factor in the amount given*. If the general practitioner is worried, then a hospital bed must be available, and in our hospital a list of the emphysematous patients who attend our clinic is kept in the receiving-room and admission is never refused. What is more, admission may be arranged through the patient's wife who notes a deterioration in her husband's condition, and it is surprising how helpful the wife can often be. With the patient in hospital we hope and pray that the antibiotic will work, because if it does our anxieties are over.

Only too frequently, however, in spite of antibiotics the patient's general condition deteriorates, the cyanosis deepens, and the drowsiness gives way to semi-coma. We have no time to wait for sputum cultures, and in any case they often come back with a "non-pathogenic" report. We may give another antibiotic in the hope that it will work and at the same time make the patient cough up his sputum, rouse him to consciousness, and relieve his anoxia. To make the patient cough his sputum up we have used aminophylline and nikethamide given in drip and intermittently, but we objected to nikethamide on the same grounds as Drs. Westlake and Campbell. However, one of us (W. H.) suggested treating these patients as in barbiturate poisoning with bemegride and amiphenazole, and after talking to Professor F. H. Shaw, of Melbourne, who assured us that amiphenazole was non-toxic even in repeated dosage, we have used it alone. It can stimulate the respiratory centre even when depressed by oxygen, there is minimal stimulation of the central nervous system other than the respiratory centre, and it is non-toxic in repeated dosages. We give 150 mg. intravenously hourly for as long as necessary. In addition to stimulating the brain and making the patient cough it causes nausea, which helps to get rid of the sputum. In this way we have, on several occasions, avoided tracheotomy, and we have given up the use of nikethamide altogether. If the patient remains cyanosed and unresponsive in spite of amiphenazole, tracheostomy must be done, more especially if oxygen therapy results in carbon-dioxide narcosis.

We would like to add a word about tracheotomy. Do it when you first think of it, because no harm is done and a delay of even hours may be too late. Do not expect that suction after tracheotomy will result in the evacuation of lots of sputum and the patient will suddenly become pink and conscious. In our experience this is rare. If, after the aspiration of secretions, the patient is obviously cyanosed, oxygen must be given by catheter resting in the tracheotomy tube, and if coma ensues then positive-pressure breathing must be given. Although it is early days, we have found the Bird Respirator* excellent for this purpose—it is cheap, compact, silent in operation, and 40% oxygen may be given. It is uncertain whether positive-pressure respiration does carry an added risk for those patients with heart failure, and if nothing is done then they die. Our most recent patient who had positive-pressure respiration was in severe heart failure and he recovered.

A word about oxygen therapy. Oxygen must *always* be given when cyanosis is severe, and if coma follows this must not be an indication for stopping the oxygen. It is an indication for intermittent therapy or some form of assisted respiration. If the oxygen is stopped the patient will become anoxic and his mental state will often improve. He may be able to talk sensibly and eat his food. A false sense of security may be engendered, and it may be decided not to resume the oxygen unless his condition worsens. When, some hours later, the patient suddenly

*Bird Residual Breather Mark 7, obtainable through Godart-Mijnhardt Ltd., Chatham, Kent.

dies, all are surprised. Therefore, if oxygen is given—even though intermittently—do not stop it until the patient is better.

In summary, then, the main attack must be on the infecting organism, and it would be a great advance if one could recognize it at once and give the appropriate antibiotic. Amiphenazole is undoubtedly our second line of attack, and our final approach is tracheostomy done early rather than late and, if necessary, coupled with the respirator. Finally, oxygen must be always given to the severely anoxic patient, irrespective of whether it causes coma or not, because the effects of severe anoxia on the brain are irreversible.—We are, etc.,

T. SIMPSON.
W. HAWKINS.

Chase Farm Hospital,
Enfield, Middlesex.

SIR,—The observations of the late Dr. E. K. Westlake and Dr. E. J. M. Campbell (*Journal*, January 31, p. 274) and in your annotation of the same date (p 289) are of interest to all those who have to deal with the acutely ill emphysematous bronchitic.

The general practitioner, when he first sees these patients with severe respiratory difficulty associated with marked bronchospasm, must turn to an easily given and rapidly effective drug. Aminophylline, given intravenously in doses of 0.25–0.5 g., restores respiratory ease almost immediately. I am never without a few ampoules, and find it of great value in the initial management of this type of respiratory emergency, so often seen in an industrial area where bronchitis is widespread. The occurrence of "smog" so quickly brings about severe exacerbations of this condition. A timely injection of aminophylline restores a patient within minutes. My experience is that a second injection is rarely needed. Treatment is continued with oral bronchodilators and antibiotics.

An incidental "tip" in the management of these cases, for which my thanks must go to Dr. T. D. Kellock, of the Central Middlesex Hospital, is the placing of a small dish containing a little household ammonia in the sick-room. This seems to neutralize some of the acidity of the "smog" atmosphere pervading the room. My patients readily testify to its help.—I am, etc.,

London, N.W.2. D. S. NACHSHEN.

Drug Treatment of Chronic Bronchitis

SIR,—Chest expansion in the chronic bronchitic patient would appear to be a matter of great importance. During the last three years I have made a practice of checking this in the chronic bronchitic and other patients. In brief, the chronic bronchitic and emphysematous patient seems to lose expansion more definitely than others—as much as 1½ in. (38 mm.) in three years—and may be left with as little as a quarter of an inch (6.4 mm.). Those with the least expansion seem to suffer more frequent and severe episodes of acute chest illness, and for this group steroids have greater value during the acute stages of illness. Antibiotics and antispasmodics are invaluable, as Dr. J. G. Scadding reports in his article (*Journal*, January 10, p. 107), but the use of steroids in addition has appeared to me to be life-saving on occasions.

Expansion can be won again where the patient performs exercises designed for this purpose and has clearly understood the nature of his problem. It cannot be regained in all cases. One feels very sadly that, had one begun three or four years earlier, the outlook for certain patients would have been far brighter. Is it the experience of other doctors that loss of chest expansion is so disastrous ?—I am, etc.,

Clapton, E.5. ALAN REZLER.

Cough Mixtures

SIR,—Seeing "Cough Mixtures," by Dr. N. C. Oswald, on the cover of the *Journal* of January 31, I turned hastily to the page (292), hoping at long last to find out what is meant by a "sedative expectorant," and why one gives a gastric irritant like ipecacuanha to cause reflex expectoration, combined with morphine to depress or annul the reflex in the same mixture. Alas (unless some Oracle speaks), my grey hairs must go down in sorrow—and ignorance—to the cremation chamber.—I am, etc.,

London, E.4. FREDERIC SANDERS.

Sulphonamide Mixtures

SIR,—Dr. B. Wolman's letter (*Journal*, January 24, p. 233) raises an interesting point of therapy in paediatrics. In this part of B.A.O.R. at least, we find invaluable a simple mist. sulphadimidin. flavoured with syrup of raspberry or blackcurrant, which we use for the majority of those upper respiratory and other infections for which specific therapy is definitely indicated. The use of antibiotics outside hospital in the vast majority of children's ailments is in any case questionable, but for these cases we have found that oral therapy is virtually as effective as parenteral, and often avoids turning the sick-room into a circus, an exhausting performance for all concerned.—I am, etc.,

Medical Branch,
H.Q. 4 Div.,
British Forces. G. P. CREAN.

Too Many Tonsillectomies ?

SIR,—I have read with great interest the contributions to the *Journal* on tonsillitis, from general practitioners. I would like to say something about this problem from a consultant's view. The assessment for the removal of tonsils is extremely difficult. Before the war, it was unusual for a child to have attacks of tonsillitis more frequently than every three or four months, but now it occurs every two or three weeks. This, I think, is due to the giving of antibiotics, especially sulphonamides. As the frequency of attack of tonsillitis is our main yardstick for operation, it will be seen that administration of antibiotics renders the assessment much more difficult.

It is my practice in these difficult cases to ask the general practitioner, where possible, to withhold antibiotics for a period of six months, and then if the attacks are still frequent, say every two months, I put the patient down for operation.—I am, etc.,

Alder Hey Children's Hospital,
Liverpool, 12. J. MCFARLAND.

Forensic Psychiatry

SIR,—Upon reading Dr. James Harper's paper on "Out-patient Adult Psychiatric Clinics" (*Journal*, February 7, p. 357), in which he advocates "the formation in this country of special clinics for forensic psychiatry" and refers to efforts being made by the

Scottish Home Department to set up clinics in Edinburgh and Glasgow, one is left with the impression that no such clinic is yet in existence.

Has he perhaps forgotten for the moment the pioneer clinic opened in London as a psychopathic clinic in 1933 by the Institute for the Study and Treatment of Delinquency, which was taken over by the National Health Service in 1948 and renamed the Portman Clinic? Its list of functions include furnishing diagnostic reports of cases referred by the courts, probation officers, and others; treatment of suitable cases; research in conjunction with the I.S.T.D.; and training of probation officers and others for additional experience, all the kind of work referred to by Dr. Harper.

The work of the Portman Clinic still goes on. So far, it remains the only specialized clinic of its kind in this country, and has attracted the interest of many psychiatrists from all over the world.—I am, etc.,

W. PATERSON BROWN,
Chairman,
Medical Staff Committee, Portman Clinic.

London, W.1.

Carbon-monoxide Poisoning

SIR,—Now that your columns are open to the question of carbon-monoxide poisoning (*Journal*, January 24, p. 234), I note that the majority of what has been written deals with acute carbon-monoxide poisoning. The question of chronic, mild, accumulative carbon-monoxide poisoning is, I am sure, of much greater importance to the health of the population at large.

The home front is very susceptible. Gas stoves in badly ventilated kitchens without exhaust fans or suitable flues, central heating installations with stack pipes running up into old chimney embrasures, "sweating" through walls into living-rooms and bedrooms; and, of course, and highly important, leaking exhaust fumes in cars, especially during the winter.

What precautions have been taken about warning the public, teaching practitioners to recognize symptoms, and providing inexpensive methods of ascertaining harmful amounts of carbon-monoxide poison, especially intermittent concentrations? The late Sir Bernard Spilsbury was emphatic that long-continued minute excesses of carbon monoxide had not any distinct separate clinical picture, but tended to increase each exposed individual's susceptibility to any latent inherent weakness. The article by Dr. L. G. C. E. Pugh (*Journal*, January 24, p. 192) gives significant point to the reality of the dangers, but nothing seems known about smaller concentrations over longer times.—I am, etc.,

C. B. HEALD.

Chipping Campden,
Gloucestershire.

P.P.L.O. in Genital Infections

SIR,—I read with great interest Dr. E. Klieneberger-Nobel's article (*Journal*, January 3, p. 19) on her extensive investigation of pleuropneumonia-like organisms in genital infections. I was rather disappointed, however, to find no mention so far of a search for antibodies in the patients' serum. The serum of all my four cases,[1] referred to by Dr. Klieneberger-Nobel, showed positive complement fixation, controls being negative. One of them was a mild puerperal infection with low-grade fever who recovered spontaneously.

Although negative serological findings would not rule out P.P.L.O. as a possible cause of non-specific urethritis, positive findings would add weight to this hypothesis and might help to distinguish between patients actually infected and those harbouring P.P.L.O. as a commensal. Melén[2] also confirmed independently, in a later paper than the one quoted by Dr. Klieneberger-Nobel, that specific complement fixing antibodies can be demonstrated in patients infected with P.P.L.O.

I must add, for the sake of colleagues working in routine clinical laboratories, that although the extremely complex medium employed by Dr. Klieneberger-Nobel was doubtless admirably suited to a special investigation, its use for routine work is not essential. It is possible to grow genital strains of P.P.L.O. on defibrinated horse-blood agar, provided that the swab is moist on arrival, and the medium is incubated for three to five days and remains moist during this period. Nagler's medium for the identification of *Cl. welchii* also supports their growth well. P.P.L.O. can be isolated from the blood by the routine "liquoid" broth method.

One further infection with positive blood-culture has been encountered since the one reported in 1955.[1] The patient was infected post-operatively following panhysterectomy for ovarian carcinoma. She was severely ill with a high fever. P.P.L.O. were isolated twice from her blood, and in almost pure culture from a high vaginal swab. Serum taken at the onset of infection and on the ninth day showed a rise in complement fixing antibody titre from less than 3 to 300. The patient recovered when treated with tetracycline, to which the organism was sensitive.

—I am, etc.,

E. JOAN STOKES.

University College Hospital,
London, W.C.1.

REFERENCES

[1] Stokes, E. J., *Lancet*, 1955, **1**, 276.
[2] Melén, B., and Gotthardson, A., *Acta path. microbiol. scand.*, 1955, **37**, 196.

Unilateral Amblyopia

SIR,—Arising out of the recent article by Mr. Robert Wellesley Cole on unilateral amblyopia (*Journal*, January 24, p. 202), the accompanying annotation (p. 221), and subsequent correspondence, we should like to make the following observations:

(1) It is of the utmost importance to have two seeing eyes, not only because of the advantages of binocular vision, nor even because many occupations demand good or equal visual acuity, but as an insurance against loss of the "good" eye. No one with experience of the misery caused by loss of an only seeing eye in adult life would underestimate the importance of diagnosing and treating amblyopia in childhood whenever possible.

(2) It is necessary that early and adequate diagnosis should be made, not only of the visual acuity, but of the patient's binocular state. Excluding pathological conditions, in which the diagnosis of amblyopia ex anopsia does not arise, cases can be divided into: (*a*) Those maintaining binocular single vision—"straight" amblyopes. (*b*) Those with a manifest strabismus in which the amblyopia is secondary to the strabismus. This is by far the larger group; many cases in which the eyes appear straight are found to have a small-degree strabismus on careful investigation.

(3) In our experience, adequate and early treatment in childhood (i.e., correction of the refractive error and closely

supervised occlusion in most instances) results in improvement in the majority of cases in both groups. We believe there is no arbitrary upper age-limit beyond which improvement in visual acuity is impossible; the deciding factors for or against treatment are rather the patient's potential binocular vision and the economic and social problems involved. If, for example, in an older patient diplopia is likely to result, treatment is contraindicated; similarly with a child taking important examinations. Careful selection of patients likely to benefit from therapy is therefore of prime importance.

(4) We would also point out that early operation for strabismus does not solve the problem of amblyopia unless binocular single vision results. An excellent appearance can result from surgery, but if the visual axes are not quite parallel and the deviation is unilateral, the development of amblyopia may continue unsuspected and undetected unless checks are made. It follows that pre-existing amblyopia can nullify the effect of surgery, and therefore adequate pre-operative treatment must be given.

In conclusion, we would suggest that the most effective way in which these patients can be supervised is by the maintenance of an adequate orthoptic service. Orthoptists, as medical auxiliaries to the ophthalmologist in hospitals and school clinics, and working in close liaison with him, can carry out the very exacting and time-absorbing tasks of assessing visual acuity, investigating binocular function, and instigating occlusion and other non-surgical (orthoptic) treatment. —We are, etc.,

JOYCE MEIN,
A. B. NUTT,

The Royal Infirmary, Sheffield. Principal, School of Orthoptics, United Sheffield Hospitals.

Cancer Survival Rates

SIR,—For expressing the results of treatment of malignant disease, Professor Sidney Russ (*Journal*, December 27, p. 1593) has objected to the use of corrected survival rates on the ground that it is possible to obtain a 10-year survival rate greater than its associated 5-year rate. But surely this is a very small price to pay when compared with the gross inaccuracies which can result from the comparison of crude survival rates uncorrected for differences in age composition. Moreover, when such an anomalous result is obtained, it is a salutary reminder of the deficiencies of the data upon which it is based.

For instance, when presenting the results of treatment of breast cancer in this hospital by age, making correction for "natural mortality," the adjusted rate exceeded 100% in one age-group. This was the oldest age-group, in which the natural mortality rate is increasing most rapidly: in fact, of 11 spinsters over 80, six had died five years from treatment, rather than the seven expected from the Life Table. No one would place much reliance upon the accuracy of a survival rate calculated on a basis of only 11 patients, but, as the tailpiece to a more substantial body of data, it does no harm. (It is in fact incorrectly plotted in our published results (Fig. 1, p. 8, *United Birmingham Hospitals Annual Cancer Report*, Volume III, 1957). As the rate for single women was 120%, it was thought to be a decimal error, and plotted as 12%.)

It is of course unusual to subdivide into so many groups when making age adjustments to the rates. If a single figure is to be used to characterize the experience of a given centre at a given time, and this figure is corrected for natural mortality by the p_0 method of Berkson, then in ordinary circumstances there is no possibility of the adjusted rate exceeding 100%, or in any way representing an absurd result. On the other hand, comparisons between different centres, and between results from the same centre at different periods of time, can be almost completely invalidated by neglecting to allow for age differences in the patients treated.

There are many adjustments which have been proposed to the crude survival rate, and with varying degrees of plausibility. I have no doubt, however, not only of the plausibility, but of the necessity, of using an age correction such as is under discussion. I have recently put together some thoughts on this subject in a contribution to a symposium on cancer edited by P. B. Kunkler and A. J. Rains, soon to be published. I have tried to advocate a return to a measure which was in use in the earlier days—namely, the median survival time. This is, of course, the time at which the survival rate is 50%, and it can also be adjusted quite simply to allow for natural mortality. If the other quartiles (times at which the survival rate is 75% and 25%) are also quoted, a very much better idea is obtained of the pattern of survival—and again the quartiles can be adjusted to allow for natural mortality. Greenwood[1] used this measure in an early publication, and I am pleased to see it used also in some recent French reports.[2] Incidentally, it is not possible to obtain an absurd result by age correction using this method.—I am, etc.,

J. A. H. WATERHOUSE.

Department of Medical Statistics, Queen Elizabeth Hospital, Birmingham.

REFERENCES

[1] Greenwood, M., *The Natural Duration of Cancer*. Reports on Public Health and Medical Subjects, No. 33, 1926, Ministry of Health. H.M.S.O., London.
[2] Bernard, P., *et al.*, *Bull. Cancer*, 1956, **43**, 296.

Traumatic Fore-quarter Avulsion

SIR,—I was very interested to read Mr. D. S. Pracy's account of traumatic fore-quarter avulsion (*Journal*, December 27, p. 1578). I can recall having two similar cases, also due to a conveyer belt, on the Witwatersrand G.M. Company and on Witwatersrand Deep G.M. Company in 1939 and 1940. The cases occurred within a week of each other.

In the first case the whole fore-quarter plus the clavicle and scapula were cleanly torn off, and the native mine-worker nearly lost his life owing to loss of blood and shock. In the second case the clavicle broke in its mid-third and left its medial half *in situ*, otherwise the avulsion was total. In this case a native boss boy was present, and, seeing the subclavian artery spurting, he rolled it up (there was a length of about 4 in. (10 cm.) of artery sticking out) and applied a pad and bandage. This case showed practically no shock and could be operated upon immediately. Both recovered.

I described these two cases at a meeting of the Transvaal Mine Medical Officers. At the previous monthly meeting another doctor described a similar case. I therefore know of three cases which occurred on the Rand Gold Mines, all within a month and all due to being caught in a conveyer belt.—I am, etc.,

Knysna, South Africa. G. D. MORGAN.

New Diet for Laboratory Animals

SIR,—Diet 18[1] was developed during the last war to meet the need for an adequate rabbit and guinea-pig ration which could be made up from the limited range of animal foodstuffs available under the severe restrictions that then existed. The diet has served its purpose well, but in recent years evidence has been

accumulating which indicates that occasional batches are responsible for breeding difficulties and mortality among the animals. It seems likely that these troubles are attributable to deterioration in certain constituents of the diet, notably those of high oil content, when these constituents are stored by manufacturers prior to preparation of the diet.

Accordingly, a new diet has been devised and is identified as Diet S.G.1. Its components are considered to be less prone to deterioration than some of those in Diet 18, and it has provisionally been adopted at this Institute as the standard ration for rabbits and guinea-pigs. Details of Diet S.G.1 and the results of feeding trials are reported in a communication that is to appear in the *Journal of the Animal Technicians Association*.—We are, etc.,

D. J. SHORT.
L. GAMMAGE.

National Institute for Medical Research, Mill Hill, London, N.W.7

REFERENCE

Bruce, H. M., and Parkes, A. S., *J. Hyg. (Lond.)*, 1945, **44**, 501.

Subjects for Harveian Orations

SIR,—Dr. William Stephenson has justly pointed out (*Journal*, February 7, p. 369) that a study of Harvey's embryological influence in France during the eighteenth century would provide fascinating material for Harveian scholars. The second of the books to which he refers, the *Art of Making Children*, was translated from *L'Art de Faire des Garçons ou Nouveau Tableau de L'Amour Conjugal*, par M*** Docteur en Medecine de l'Université de Montpellier. (A Montpellier. Chez François Maugiron. 1748.) It is generally attributed to Michel Coltelli, who published under the name of Michel Couteau-Procope. He was born in Paris in 1684 and died there in 1753. Trained as a priest, he gave up theology for medicine, and also took an active interest in the literature of his day. He published poems and plays (one of which was acted in London in 1719), as well as several medical works. One of these was a discussion of the best means of establishing understanding between physicians and surgeons (Paris, 1746). There is a copy of the original French of Coltelli's book in the Wellcome Library. It is indeed of the greatest interest to anybody interested in the embryological controversies of the time.—I am, etc.,

F. N. L. POYNTER.

The Wellcome Historical Medical Library, London, N.W.1.

Hospital Decoration

SIR,—Why need Dr. John H. Burkinshaw (*Journal*, January 24, p. 237) drag in Picasso *et al.*? Surely these gentlemen get enough publicity already? Since he derived such pleasure as a child from his patterned wall-paper, is it not likely that present-day children would be equally pleased with something similar? They might of course need to be reassured that it was "contemporary."

Entering a small restaurant lately that had been redecorated, my septuagenarian companion exclaimed: "Why, they've got a paper just like I had in my bedroom as a girl." The young lady who served us, however, assured us it was "contemporary."—I am, etc.,

London, N.W.2. R. J. CLAUSEN.

Obituary

Sir JOHN TAYLOR, C.I.E., D.S.O., M.D., LL.D. D.P.H.

Major-General Sir John Taylor, who had had a distinguished career in the Indian Medical Service, died in London on February 7, aged 74. Director of the Central Research Institute at Kasauli for 12 years, he was one of the most illustrious members of the now small band of I.M.S. officers who made outstanding contributions to medical research in India.

John Taylor was born on February 14, 1884, and received his medical education at Glasgow University, obtaining the M.B., Ch.B. degrees in 1905 at the early age of 21. The following year he entered the Indian Medical Service, having taken first place at the entrance examination at a time when competition was exceptionally keen. He proceeded to the M.D., with honours, in 1913, and took the D.P.H. of the English Royal Colleges in the same year. After completing two years' military service in India he was transferred to civil employment at the Haffkine Institute, in Bombay, which was then still in its formative years.

The recent reintroduction of bubonic plague to India about that time created a public-health problem of the first magnitude, and it was to the investigation of this disease that Taylor gave his attention. He was a member of the Indian Plague Commission set up in 1908 under the leadership of the late Sir Charles Martin, and, as is well known, the work of this commission resulted in the discovery of the mode of transmission of plague by the rat-flea. Taylor was also much concerned with the preparation of plague vaccine, and throughout his long career in India maintained his interest in plague, on which he was a recognized authority. Many years later, while director of the Haffkine Institute, he compiled a monograph entitled *Haffkine Plague Vaccine*, which appeared in the special memoir series of the *Indian Journal of Medical Research*. In his early years in India Taylor travelled extensively, mostly on horseback, through plague-infested territories, and it was during this time that he developed his great talent for riding, fishing, and shooting.

Taylor reverted to military duty from 1914 to 1920, and served with great distinction during the first world war, being mentioned in dispatches on several occasions and being awarded the D.S.O. in 1915 for gallantry in the field. At the end of the war he was appointed first medical officer of health of Bagdad after the city's occupation by British Forces.

On reversion to civil employment he acted as public health commissioner with the Government of Assam for two years. He then joined the staff of the Pasteur Institute of Burma and so commenced his long and uninterrupted association with research laboratories. In 1925 he became director of the Pasteur Institute in Rangoon and also held the appointment of professor of pathology in the Medical College, Rangoon. His service in Burma provided him with wide and varied experience of general bacteriology and pathology, and gave him the opportunity for special investigation into rabies, cholera, leptospirosis, and beri-beri. During this period he produced two further monographs entitled *Preliminary Enquiry into Beri-beri in Burma* and *Leptospirosis in the Andamans*.

Taylor's wide and varied experience in India and Burma and his flair for leadership and administration made him exceptionally suited for the directorship of the Central Research Institute, Kasauli, where he succeeded Sir Rickard Christophers in 1932, and he held the post with distinction for the next 12 years. During the period of his directorship extensive alterations and additions were made to the Institute, and, among other changes, the Pasteur Institute of India was absorbed into the Central Institute, where it was

suitably housed in new and up-to-date premises. While at Kasauli Taylor made improvements in all directions. He carried out personal researches on snakes and snake venoms and was responsible for concentrating and refining anti-venom serum. He also led a strong team of workers on the cholera vibrio, investigations in which he was closely associated with the late Bruce White of the National Institute for Medical Research.

Taylor also took a special interest in T.A.B. vaccine, and the improvements which were effected in this important product were reflected in the outstanding success which Kasauli T.A.B. vaccine achieved in the protection of both civil and military personnel during the second world war, particularly after the evacuation of Burma and in the subsequent campaigns in Burma and other eastern theatres of war. During this period his name appeared on many scientific papers. He was a prominent and popular member of the Army Pathology Advisory Committee in India and, after his retirement, of the Army Pathology Advisory Committee at the War Office. For many years he was a prominent figure in the affairs of the Indian Research Fund Association, being a member both of its governing body and of its scientific advisory board. He exerted a powerful influence on the deliberations of both of these bodies, which were primarily responsible for the financing, orientation, and over-all direction of medical research in India. He was also editor of the *Indian Journal of Medical Research*, published under the auspices of the Indian Research Fund Association. This was work which he enjoyed and for which he was particularly suited, being by nature an unusually sound, though sometimes devastating, critic. Taylor was largely responsible for the introduction of legislation governing the manufacture and sale of biological products in India. He set up a biological standards laboratory at the Central Research Institute and took a prominent part in drafting the legislation in the relevant sections of the Drugs Act. For his work at Kasauli he was appointed C.I.E. in 1937 and was created a knight in 1942, having been promoted successively colonel and major-general while at Kasauli. He was Honorary Surgeon to the King from 1939 to 1941 and Honorary Surgeon to the Viceroy from 1936 to 1941. Among the many honours he received, the honorary LL.D. degree of Glasgow University conferred on him in 1945 was perhaps the one which he prized the most.

On his retirement from India in 1944 he took up part-time work with the Medical Research Council, where his wide knowledge and experience of medical research in the tropics was of special value at a time when strenuous efforts were being made to foster medical research in the Colonies. He served as joint secretary of the Colonial Medical Research Committee and as liaison officer between the Commonwealth Relations Office and the Indian Council for Medical Research. His long experience of editorial work was also valuable in connexion with the M.R.C.'s numerous reports and publications. He was an enthusiastic Fellow of the Royal Society of Tropical Medicine and Hygiene and served on its council for several years, including terms as vice-president and trustee.

Sir John Taylor's outstanding contributions to medical research depended more on his ability as a leader and administrator than on his own original observations. He was a man of small stature, and, despite a rather direct manner, he was a very approachable and friendly person who was always ready to help others. With his extremely quick brain he had a flair for getting to grips with the fundamentals of any problem. A fast rather than a hard worker, he could get through more work in a few hours than most people could manage in a long day. This was well suited to his mode of life, for he enjoyed his leisure hours to the full. In his earlier years he devoted much time to the training of steeplechasers and achieved great success as owner, trainer, and jockey, and whenever opportunity offered he was a keen rider to hounds. He was also an excellent shot, but his ruling passion was fishing, a sport which he continued to enjoy almost to the time of his death. He was extremely proficient in fly-tying, a hobby which he enjoyed throughout his service in India and which he continued at the Flyfishers' Club, of which he was a past president. One of his masterpieces was a new salmon fly which he christened "Old Glory" and which he tied specially for presentation to the then American Ambassador, the well-known fisherman, Mr. Lewis Douglas.

Sir John Taylor was a widower, his wife, formerly Miss Katherine Monro, a member of the family of well-known anatomists in Edinburgh, having died about five years ago. His only son was killed in Normandy in 1944, and he is survived by twin daughters, both married.

M. L. A. writes: By the death of Sir John Taylor the Central Research Institute, Kasauli, has lost one of its distinguished directors, who guided its activities from 1932 to 1944 and who rendered invaluable service to the Government of India for 38 years. Sir John Taylor was a man of exceptional gifts whose high example of devotion to duty would be hard to follow. During the difficult period of the war when his staff was greatly depleted—many of the senior officers in charge of the various departments of the Institute having been called up—he threw himself with untiring energy into his work. Under his leadership the Institute was able to supply enormous quantities, nearly a million doses per month, of prophylactic vaccines and sera to the Armed Forces in India and abroad. His enthusiasm for work was infectious, and he was genuinely admired, not alone for his ability as an administrator but as a research worker whose chief interests lay in preventive medicine in the tropics. Cholera research remained his favourite subject of study for a number of years, not with a view to acquiring more basic information on the bacteriology of cholera vibrio, or its chemical structure and metabolism, etc., but to utilize the knowledge gained as a basis for application of preventive measures.

Until the last war India was dependent for most of her requirements of biological products on foreign imports. There was no organized attempt to assess the quality of these products, and the country was for years flooded with substandard preparations of both indigenous and foreign origin. Sir John Taylor played a very important part in organizing and developing a machinery—the Drugs Act, 1940—for the assay and standardization of biological products, and thus laid the foundations of the Central Drugs Control Laboratory in India and helped the industry for the manufacture of biological products of standard specifications in the country.

A strict disciplinarian, but a man of generous disposition, Sir John Taylor was always ready to spend himself in the interests of others who were willing to learn. He will be greatly missed by his colleagues and the staff who had the privilege of working with him.

WILLIAM WASHBOURN, C.B.E., M.R.C.S., L.R.C.P.

Mr. William Washbourn, consultant surgeon to the Royal Infirmary, Gloucester, died at his home in Gloucester on February 4, aged 96.

William Washbourn, a member of one of the oldest families in the city of Gloucester, was born on June 15, 1862. He began the study of medicine at University College and went on to take his clinical training at University College Hospital, qualifying in 1884. After holding the appointment of house-surgeon at his teaching hospital he returned to the city of his birth and was appointed house-surgeon to the Gloucestershire Royal Infirmary. His surgical ability was soon recognized, and, after being assistant surgeon from 1894, he was elected to the staff as surgeon in 1898. He was appointed C.B.E. in 1920 in recognition of his services during the first world war as surgeon to the City General Hospital, which was taken over by the British Red Cross Society and of which he was the organizer. When he retired from the surgical staff he was made deputy chairman of the board of governors of the Gloucestershire Royal Infirmary, and in the second world war deputized for the chairman, Rear-

Admiral Sir Richard Bevan, who was called to active service. He had been actively connected with the hospital he loved since 1880, a period of nearly eighty years.

A. A. writes: Mr. William Washbourn was a remarkable man. He would not retire from practice at the normal age, and saw his last patient on his 95th birthday. He drove his car until he was 90. A very efficient surgeon, he was ahead of his time in his young days, and, by gaining the confidence of the medical practitioners for many miles around Gloucester, he had a very large surgical practice. One of his characteristics was his meticulous punctuality: he would always arrive five minutes early, both for his hospital sessions and his private consultations. Like his famous brother, Dr. J. W. Washbourn, assistant physician to Guy's Hospital from 1895 to 1902, he was always interested in bacteriology and to the end kept himself up to date. In his recreation he was a crack shot with both rifle and gun, being a prize-winner at Bisley, and also a very fine dry-fly fisherman. He leaves a widow and a son who is a Freeman of the city of Gloucester.

J. R. CANDY, M.B., Ch.B., B.Sc.

Dr. J. R. Candy, who was in general practice at Tadworth, Surrey, for many years, died after a short illness at Epsom District Hospital on January 1. He was 59 years of age.

Born in Londonderry on January 10, 1899, James Robert Candy studied at Glasgow University, where he took his B.Sc. before returning to Northern Ireland to train as a naval architect. It was not long, however, before he decided that his future lay in medicine, and, with the encouragement of his brother, the late Dr. Thomas Candy, of Newport, he became a medical student at the University of Edinburgh, where he graduated M.B., Ch.B. in 1931.

Five years later he settled in Tadworth, and rapidly built up a thriving practice. An unfailing sense of humour and quick sympathy and understanding of their problems endeared him to his patients, not only as a doctor but as a personal friend, and it is as a friend that he will be remembered by them. In recent years he became medical officer to the Distillers Co. Ltd., Heinemann's Press, and Precision Grinding Ltd. His scientific training and medical experience made him particularly suitable for these posts, in which he earned the respect and affection of staff and employees alike. To his colleagues he was a charming and amusing companion, and with them he spent many of his leisure hours on Walton Heath golf course, where he was a familiar figure. He played a good game, to which several trophies bear witness. A member of the Medical Golfing Society, he was a captain of the London Irish Medical Golfing Society. He will be sadly missed by a wide circle of friends, and to his widow and only daughter we extend our deepest sympathy.—D. M. D.

KATHLEEN M. WELDON BELL, M.B., B.S.

Dr. Kathleen Bell, consulting anaesthetist to the Royal Victoria Infirmary, Newcastle upon Tyne, and to the neurosurgical unit at Newcastle General Hospital, died on January 27 at the age of 59. Her husband, Dr. D. G. P. Bell, survived her by only three days.

Kathleen Mary Weldon Watts was born at Cullercoats, Northumberland, on March 3, 1899, and was educated at Polam Hall, Co. Durham, and at the Central High School in Newcastle upon Tyne. Like her brother, Mr. Weldon Watts, immediate Past-President of the British Medical Association, she became a medical student at the Newcastle Medical School. After graduating M.B., B.S. from Durham University in 1920, she spent some time in resident posts at her teaching hospital, the Royal Victoria Infirmary. She married Dr. Douglas Bell in 1924, and lived at Throckley, in the Tyne valley, where she brought up her family, a son and a daughter, now both married. Though always interested in anaesthesia, it was not until about 28 years ago that she began to practise as an anaesthetist.

G. F. R. writes: It was in the early 1940s that Dr. Kathleen Bell came to the department of neurological surgery at the Newcastle General Hospital, and she was soon appointed head of the anaesthetic section. It was then that she and I started a friendship which developed until she died. Regarding the extent of her scientific knowledge, no one ever knew, for the good reason that she never told anyone. But on the quality of her practical skills there was no doubt. She was a genius "with green fingers," as anyone who worked with her will testify. She became expert in cooling anaesthesia, and difficult cases would channel her way from many a surgical source. However, she will not be remembered so much for her technological skills as for her dignity, personal charm, and kindliness. Her photograph will hang in the new Institute of Neurology, and I dare hazard a guess that many an eye will be damp when it first catches a glimpse of that tribute to the memory of Kathleen Bell. She was held in dear affection by many surgeons, nurses, secretaries, and patients now scattered over this country and many others abroad.

D. G. P. BELL, D.S.C., M.D.

Dr. D. G. P. Bell, a deputy commissioner for medical services under the Ministry of Pensions and National Insurance, Newcastle upon Tyne, died on January 30, three days after the death of his wife, Dr. Kathleen M. Weldon Bell. He was 62 years of age.

Douglas George Patrick Bell was born at Fulforth, Co. Durham, on December 24, 1896, the son of J. P. F. Bell, a Fellow of the Royal Society of Edinburgh. The first world war interrupted his medical studies at the Newcastle Medical School, and he served in the Royal Navy from 1915 to 1919. For his gallantry during the Battle of Jutland he was awarded the Distinguished Service Cross. At that time, at the age of 19, he was serving as a surgeon-probationer in the destroyer H.M.S. *Spitfire*, and during the action he not only helped the wounded but, to save the life of one casualty, amputated a limb single-handed and in the dark. After the war he resumed his studies, and graduated M.B., B.S., with honours, from Durham University in 1919. He was awarded the Charlton, Goyder, and Philipson scholarships, the latter as the undergraduate who obtained the highest marks at the final examination. Four years later he proceeded to the M.D. After graduation he held the appointments of house-surgeon and house-physician at the Royal Victoria Infirmary, Newcastle upon Tyne, and medical officer in the electrotherapy department of the Ministry of Pensions Hospital, also at Newcastle. In 1922 he entered general practice at Throckley, near Newburn-on-Tyne. After some years he decided to accept full-time service with the Ministry of Pensions, and after the second world war he eventually became a deputy commissioner for medical services.

W. A. H. writes: It is with deep regret that we heard of the sudden death of Dr. D. G. P. Bell, a few days after the death of his wife. 'D.G.P.," as he was known to all his friends, seemed to have all the attributes which make for success. He was extremely handsome, and he and his wife were outstanding at any social function. He had a distinguished career as a student, and the award of the D.S.C. while he was serving as a surgeon-probationer was a notable honour. An excellent sportsman, he was a lover of country life and the open spaces, and he much enjoyed a day amidst the grouse and pheasants. He was an esteemed member and regular attender of the Diners' Club in Newcastle, and we shall greatly miss his dry humour and handsome presence at these meetings. We extend our deepest sympathy to his son and daughter.

J. GRAHAME CAMPBELL, M.D.

Dr. J. Grahame Campbell, who was a well-known general practitioner and radiologist in Rotherham for very many years, died in hospital at Poole, Dorset, on

January 19 after a long illness. He was 86 years of age.

James Grahame Campbell was born on February 4, 1872, the eldest son of an eminent Belfast barrister, and was educated at the Methodist College and the old Queen's College, Belfast. He graduated M.B., B.Ch. from the former Royal University of Ireland in 1905, proceeding to the M.D. three years later. After various house appointments in Belfast, London, and Sheffield, and an extended trip round the world, he entered general practice at Rotherham in 1907. With a vast fund of general knowledge, a keen sense of humour, and a nature which was generous to the extreme, he could not fail to be a success in general practice. A first-class clinician of the old school, he kept himself up to date with modern trends in medicine. Soon after the first world war he became interested in radiology, and for twenty years was radiologist to the Rotherham and Mexborough hospitals. A member of the British Medical Association for over fifty years, he was chairman of the Rotherham Division from 1935 to 1937. He retired from practice in 1947, but remained active physically and mentally up to a few months before his death.

E. C. writes: With the death of Dr. J. Grahame Campbell the profession has lost another general-practitioner specialist, that fast-disappearing body of men that many of us consider were the salt of the profession. For a generation he ran the radiological department of the Rotherham Hospital in the days when it was a voluntary hospital, and although the work then was not so highly geared scientifically, we did not seem to have the difficulties and frustrations of the present day. Dr. Campbell was a kindly, gentle, lovable man, and it was my privilege to have his friendship. He was greatly blessed with a loving wife and talented children who filled his life with happiness and his home with cheerfulness, and foreigners—sometimes his home was rather like an international youth hostel. Fond of music, pictures, and books, his main interest in life was his family. With the coming of the National Health Service he retired to Parkstone, in Dorset, where he owned and ran a charming old hotel, where I was received with open arms. It gave us all great pleasure that he was so happy, well cared for, and successful in his so-called retirement. Dr. Campbell retained his spirit of youth until his last illness, and his mental and physical activity were remarkable for so old a man. He leaves a widow, a son who is a consultant radiologist, and two daughters, one of them a consultant anaesthetist. To them we offer our sincere sympathy in their bereavement.

H. S. ATKINSON, M.B.E., B.M., B.Ch.

Dr. H. S. Atkinson, who was in general practice at Redhill, Surrey, for over twenty years, died suddenly at the London Hospital on February 9. He was 53 years of age.

Henry Sidney Atkinson was born on October 16, 1905. From Oxford he went on to the London Hospital to receive his clinical training, and qualified M.R.C.S., L.R.C.P. in 1929. Two years later he obtained the degrees of B.M., B.Ch. After holding a number of appointments at the London Hospital, including that of medical first assistant and registrar, he entered general practice at Redhill in 1934. As a flying officer in the Royal Air Force Volunteer Reserve he was immediately mobilized on the outbreak of the second world war in 1939. For most of the war he served as a medical specialist in the R.A.F., but he was forced by ill-health to relinquish his commission in April, 1945. He then returned to his practice at Redhill, where he was also physician to the East Surrey Hospital. In addition, he was medical officer to the Reigate and Banstead branches of the London Hospital. In the Coronation Honours of 1953 he was appointed M.B.E. (Civil Division) for his services as chairman of the committee of the Reigate and Redhill squadron of the Air Training Corps.

Dr. GILBERT RUSSELL writes: Henry Atkinson was a living proof that the best kind of family doctor can triumph over the difficulties, stresses, and strains of general practice in the post-war world. He was a modest man; some may have thought him a shy one, but he had a warmth and an affection which, especially in recent years, were increasingly manifest. Courteous, capable, confident in his professional work, interested and knowledgeable in many fields beyond it, invariably loyal to his colleagues, and unwearying in his care for his patients, he had by virtue of these qualities, and by these alone, won a unique position and widespread influence in the neighbourhood where he lived and worked for more than twenty years. It is only after his sudden death, at the height of his powers, that many of us have realized how irreplaceable such men are. It is often written of the dead that they were unsparing of their time and energy in the service of others: of Henry Atkinson this is simply true. He often looked as though his physical strength was unequal to the demands he made on it, and he worked when another man would have taken to his bed, but always without hurry, without impatience. And somehow he found time to entertain, with his wife, a host of friends who offer to her and her family their deepest sympathy.

WILLIAM STARKEY, M.B., B.Ch.

Dr. William Starkey, formerly medical superintendent of Plymouth Mental Hospital, Blackadon, Ivybridge, South Devon, died in hospital at Llandudno on January 19, in his 85th year.

William Starkey was the son of Dr. William Starkey, of Dublin, a noted physician of his day. Educated at Wesley College, Dublin, he showed an aptitude for literature, in which, however, he was excelled by his only brother, who became the distinguished Irish poet and wrote under the name of Seamus O'Sullivan. His brother predeceased him by one year and was greatly missed. William Starkey received his medical education at the Royal University of Ireland, graduating M.B., B.Ch. in 1900. Some time afterwards he became medical officer at Downpatrick Mental Hospital under the superintendency of the late M. J. Nolan. There he made his mark, and his services were soon so valued by Dr. Nolan that he was strongly urged to remain at Downpatrick with a view to taking over the superintendency. Wisely, however, he did not accept this advice, but came to England about 1902 as a medical officer at Prestwich Mental Hospital, Manchester, where he later became deputy medical superintendent. He left Prestwich in 1916 to become medical superintendent of the Plymouth Mental Hospital, where his main work in psychiatry was done, and where to-day he is still remembered as an able and kindly administrator who never lost the human touch.

D. J. O'C. writes: Dr. William Starkey was a very gifted man with widespread literary interests, a collector of first editions, a brilliant conversationalist, and a knowledgeable naturalist. He was also a pianist of distinction. In his younger days he was a scratch golfer and could make a 100 break at billiards. He was still a relatively young man when he retired from the post at Plymouth, and, on the invitation of his friend, the late Dr. D. F. Rambaut, he accepted an appointment as resident medical officer at the seaside home at Llanfairfechan of St. Andrew's Hospital, Northampton. There his many talents found free expression, and he was soon recognized as a devoted and dedicated physician by the patients for whom he cared. When he retired from this post in 1943 he decided to make his home at Llanfairfechan, but he continued to work as neuropsychiatrist for the Ministry of Pensions of the North Wales area until his 80th year. A member of the British Medical Association for nearly fifty years, he was chairman of the North Caernarvon and Anglesey Division in 1937–8.

Dr. Starkey married Miss Phyllis Tate, the Matron of Plymouth Mental Hospital, and she was a devoted wife and his constant companion, sharing his interests and contributing

much to the general enjoyment of anyone privileged to meet them in their home at Llanfairfechan. In his later years he was always delighted to receive his former friends. During the past two years he became increasingly infirm but retained his full intellectual powers to within a few days of his death, which he faced with courage, assisted by the fact that he had been a sincere and practising member of the Church of England throughout his life: from this source he found, at the end, comfort and consolation.

Medico-Legal

ANAESTHETIST NOT NEGLIGENT

[FROM OUR LEGAL CORRESPONDENT]

On January 16 the Court of Appeal allowed the appeal of the North Liverpool Hospital Management Committee and Dr. Edward Otis Pratt against a judgment of Mr. Justice Elwes at Liverpool Assizes last June. There £435 damages had been awarded a Mrs. Alice Williams in an action for negligence in the administration of thiopentone by Dr. Pratt for a varicose vein operation. The case against the committee was that they were vicariously responsible for Dr. Pratt's negligence.

Extravenous Injection of Thiopentone

Mrs. Williams was exceedingly fat, weighing, according to Dr. Pratt's estimate, 17 or 18 stone (108–114 kg.). In order to assist locate a vein for the thiopentone injection the theatre assistant applied a manual tourniquet to her right arm, and Dr. Pratt found the vein on the first or second prick of the needle, which he inserted obliquely. He then aspirated in order to make sure he was in the vein, and, finding there was blood in the syringe, injected up to 5 ml. of the thiopentone solution. This produced no visible anaesthetic effect on Mrs. Williams, so he withdrew the needle and held it up to see if it was blocked. At this stage both Dr. Pratt and Mrs. Williams were able to see discoloration of the contents of the syringe by blood. Thereafter Dr. Pratt made numerous further efforts to find a vein first in her right and then in her left arm, but was unable to do so. He concluded that a great portion of the 5 ml. he had injected must have gone into the tissues instead of the vein, and injected saline solution at the site to minimize damage by the thiopentone. But as a result of the thiopentone entering the tissues an abscess developed.

The criticism made of Dr. Pratt's technique was twofold. It was said that in order to be sure that the needle kept in the vein the anaesthetist ought to aspirate at intervals while giving the injection; but on that point the trial judge found in favour of Dr. Pratt, since the preponderance of medical evidence was in his favour.

The second failure of technique alleged was the judge's finding that Dr. Pratt had failed to ask Mrs. Williams if she was suffering any pain. Most of the expert evidence was to the effect that to ask was a proper and necessary precaution, and the judge had held that Dr. Pratt had been negligent in not doing so. The fact was, however, that Mrs. Williams felt no pain during the injection, nor was there any swelling. So, if it was a failure in technique not to ask the patient if she suffered any pain, it was a failure which did not affect this case, because her answer had she been asked would have been, No.

The Court of Appeal decided accordingly that there was no basis for a finding of negligence against Dr. Pratt, with the result that his appeal, and consequently the appeal of the Management Committee, succeeded. The Court ordered the damages which had been paid into court to be paid out to the appellants. The appellants did not ask for costs again Mrs. Williams, who was an "assisted person" under the Legal Aid and Advice Act, 1949.

Medical Notes in Parliament

HEALTH SERVICE ESTIMATES

An estimated provision of £477,549,810 for the Health Service in England and Wales for the financial year 1959–60 is shown in the Vote on Account published on February 11. The provision for the Scottish Health Service is given as £59,585,155. The total net estimates for the current financial year (1958–9) are set out as £489,049,136 and £60,629,500 respectively. The two sets of figures are not this year comparable, since some services previously borne on these Votes are now included in the general Exchequer grant for local authority services, for which £448m. are provided for 1959–60, plus £54,727,000 for Scotland. Items separately shown in the Vote on Account include £26,887,485 for the Ministry of Health (compared with £27,277,045 in the previous year); £3,518,250 for the Medical Research Council (£3,137,100); and £5,160,450 for the Department of Health for Scotland (£5,105,665).

HOSPITAL TREATMENT OF CHILDREN

Lord CROOK invited the House of Lords on February 12 to declare: that it was essential to the future of the Health Service to retain the existing large centralized children's hospitals, alike in the interests of (*a*) the most efficient treatment of children, (*b*) effective continuation of the Register of Sick Children's Nurses, and (*c*) implementing the policy of education of children in hospitals, as desired by the Minister of Education, the Minister of Health, and the county education authorities.

Queen Mary's Hospital, Carshalton

Lord Crook explained that he moved this because of the knowledge that the Minister of Health was considering a large-scale change that would set back the clock 50 to 100 years, and doing so for reasons not of policy but of expediency. In this the Minister would be flying in the face of his recent declaration agreeing with the recommendations of the Royal College of Physicians. The Minister had been invited to close Queen Mary's Hospital at Carshalton, Surrey, the largest and probably the best-equipped children's hospital in Britain, and perhaps in Europe. Since the regional board took it over in 1948 they had built up a service catering for all types of disease in childhood. Since he (Lord Crook) had given notice of this motion the Surrey Medical Committee had unanimously protested against the proposed closure, and the Croydon Medical Committee had passed a resolution deploring the proposal. The Surrey Education Committee had written informing the Minister that it was impossible for them to provide anywhere else anything like the service given at Queen Mary's.

Behind the suggested closure, Lord Crook said, lay only one thing: the lack of provision for capital expenditure to rebuild the Fountain Hospital for Mentally Deficient Children at Tooting. Queen Mary's was to be broken up, and everything it stood for destroyed, so that a new home might be found for the mentally deficient children at no apparent capital cost. The Fountain Hospital, erected as a temporary structure during a fever epidemic towards the end of the last century, was in such disrepair that it must either be rebuilt or an alternative way out found. The way out found for the Minister was to abolish Queen Mary's and spread its children among the 30 hospitals in the region, none of them equipped to give the kind of treatment they had at Queen Mary's. The hospital had 550 beds, with 150 in reserve, of which 400 were occupied.

In the last 12 months for which figures were available there was a turnover of 4,307 children, aged from a few days to 16 years.

Lord AMULREE supported the motion, with the reservation that the Minister should be able to make changes in hospital planning according to new circumstances. In other countries —the United States, France, Scandinavia—the tendency was for children, where possible, to be taken care of in special children's hospitals. It would be impracticable to treat all children in specialist hospitals. But he hoped the Government would not be carried too far along the line of changing the big children's hospitals into something else and putting the children in the special departments of general hospitals.

Need to be Flexible

Lord COHEN OF BIRKENHEAD said the function of Queen Mary's had significantly changed. When he knew it 30 years ago it was a long-stay hospital. Now nearly 80% of the children there stayed for less than a month, which meant that they could be dealt with satisfactorily in acute general hospitals with adequately equipped children's units. There was clearly a need, in view of the changing demographic and disease pattern, for a review by all hospitals and regional boards. The first principle should be that they must look for other possible uses if the need for the specific use for which a hospital was built had so lessened that it had a significant number of surplus beds; and the second, that they must ensure, if children were displaced from a hospital, that they were not deprived of any service at the highest level necessary for their cure and rehabilitation.

It would be reckless folly to concur in the general motion Lord Crook had moved—which was what they were discussing, not the specific instance he had raised—and impose on the Minister a rigidity which ignored the changing scene of hospital needs and resources.

Lord UVEDALE urged that the difficulties at the Fountain Hospital should be dealt with by the construction of a new hospital at Tooting; it could be done in sections, over a course of years.

Long-stay Children the Problem

Lord TAYLOR calculated, from an analysis made at the Nuffield Provincial Hospitals Trust of admissions of children to hospital, that in a 400-bed general hospital the need was for a children's unit of 52 beds—16 medical, 16 surgical, and about 20 for tonsils and adenoids. Most of the acute cases at Queen Mary's Hospital, he thought, could be looked after in children's blocks in local hospitals. The long-stay children presented a real problem: he mentioned muscular dystrophy, cerebral palsy, and rheumatic cases. Whatever happened at Carshalton in future, it was important that those units should not be split up.

The EARL OF ONSLOW, Captain, Yeomen of the Guard, stated that the suggestions put forward by the regional hospital board in relation to Queen Mary's Hospital were under consideration by the Minister, who had deferred his decision until he had heard what was said in the debate.

Lord CROOK withdrew his motion.

QUESTIONS IN THE COMMONS

M.R.C. Review of Research on Mental Illness

Mr. N. DODDS (Erith and Crayford, Lab.) asked the Minister of Health, as representing the Lord President of the Council, if he was aware of the concern arising from the inadequate provision for research into mental illness; and, in view of the seriousness of the situation revealed by the survey carried out by the General Register Office and the Royal College of General Practitioners, if he would state what action it was proposed to take commensurate with the size and importance of the problem.

Mr. D. WALKER-SMITH, replying on February 13, stated that the Medical Research Council were engaged on a full-scale review of policy in relation to mental health research, and the completion of this review should be awaited before any statement along the lines suggested could be considered.

"Secretaries Superintendent"

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked the Minister of Health if it was with his approval that the secretaries of certain hospitals were now designated secretaries superintendent.

Mr. WALKER-SMITH: I have recently become aware of the use of this title, but it is not in any way subject to my approval.

Ambulance Arrangements

Mr. ROY MASON (Barnsley, Lab.) asked the Minister on February 10 if he would make inquiries into the arrangements existing between general hospitals and their respective ambulance services with a view to obtaining a better co-ordinated effort for the conveyance of patients over long distances. Mr. WALKER-SMITH replied "No." The responsibility in this matter was well defined, and it was the practice of the responsible ambulance authority and the requisitioning hospital to consult each other when necessary on any special provision required on the journey. Mr. MASON then asked if the Minister would bring to the notice of all hospital boards the recent journey from Wolverhampton to Barnsley of Mr. J. W. King, and the urgent need to improve this service. Mr. WALKER-SMITH said he did not think that to be necessary. The ambulance authority concerned had already instructed its staff in the right procedure in such cases.

Mr. MASON asked to what extent it was the present policy of the Ministry to ensure proper co-ordination of ambulance services and general hospital requirements; and what proposals the Minister had in mind to better this service. Mr. WALKER-SMITH: The need for co-operation has been stressed in advice to both local health authorities and the hospitals. I have no evidence that this advice is being ignored.

Hospital Facilities on Skye

Mr. NEIL MCLEAN (Inverness, Con.) aked the Secretary of State on February 11 whether he had considered the report about the proposed location of the new hospital for Skye made by the two senior officials who visited Skye to obtain the views of the local people.

Mr. J. S. MACLAY stated that he had asked the Northern Regional Hospital Board to prepare proposals to provide for (*a*) improvements in the existing facilities at the Broadford Hospital and an extension of the in-patient facilities to enable the hospital to deal with surgical cases from all parts of Skye and the adjoining mainland and with medical and maternity cases from the south of Skye and the adjoining mainland; and (*b*) a new and smaller unit at Portree for the northern part of the island containing facilities for the diagnosis and treatment of out-patients, a few beds for general medical cases which could be treated by general medical practitioners, and a small maternity unit; the existing maternity hospital at Uig would then be closed. He was satisfied that when this new provision had been made the hospital facilities in Skye would meet all the needs of the people, both in Skye and the adjoining mainland, which should be met locally, and that this disposition of the facilities between Broadford and Portree was the best that could be made in the special circumstances of the area.

Merit Awards

The MINISTER OF HEALTH was asked on February 17 for details about the number of specialists and consultants receiving merit awards in each region, and the cost. The information he gave, in reply to Mr. D. HOWELL (Birmingham, All Saints, Lab.) was that the number of awards at the end of 1958 was: 279 at the rate of £2,500, 698 at £1,500, and 1,397 at £500. Payments made in respect of awards in 1958 were estimated to total approximately

£1,986,000. The number of consultants receiving merit awards in the various regions at the end of 1958 was:

Hospital Region	*Award Holders*
Newcastle	137
Leeds	111
Sheffield	136
East Anglian	66
Metropolitan regions	1,216
Oxford	98
South-western	131
Wales	110
Birmingham	182
Manchester	147
Liverpool	95
	2,429

The figure for the four metropolitan regions cannot be split, as many consultants work in more than one of these regions. For the same reason the total includes some duplication; the number of awards in payment is 2,374.

The minimum sums payable by way of awards are £500 for whole-time consultants and approximately £57 for part-time consultants and the maximum sums are £2,500 for whole-time consultants and approximately £2,160 for part-time consultants. Recipients of awards at the higher rates have their basic salary scale abated.

The average awards payment is estimated to have been about £857 in 1958. This does not take account of the abatement of basic salary that operates with awards at the higher rates.

He also stated that the available information was that there were about 2,200 whole-time consultants and senior hospital medical and dental officers at the end of 1950; 3,166 at June 30, 1955, and 3,192 at September 30, 1957.

Ministry's Statistical Branch

Mr. A. BLENKINSOP (Newcastle upon Tyne, East, Lab.) asked the Minister what progress had been made in establishing a central research and intelligence section in his department capable of undertaking the studies recommended by the Guillebaud Committee. Mr. WALKER-SMITH: A Statistical Branch has been established with chief statistician, four professional statisticians, and lay staff. The branch is wholly engaged on statistical inquiries and research of a kind which should lead ultimately to the provision of information of the type recommended by the Guillebaud Committee.

Glasgow Radiotherapy Institute

Mr. W. HANNAN (Glasgow, Maryhill, Lab.) asked the Secretary of State for Scotland if it was still his intention to build a major radiotherapy institute in Glasgow for advanced techniques and research, to serve the population of the Western Region and in some respects the whole of Scotland.

Mr. NIXON BROWNE, Under-Secretary, Scottish Office: Yes. Work is expected to start this year on a major radiotherapy unit at the Western Infirmary. The plans for a second unit associated with the Royal Infirmary are well advanced.

Mr. HANNAN recalled that in a letter of March 27, 1957, it was indicated that there was to be an institute co-ordinating the cancer services in Glasgow. What the Under Secretary had said was most disappointing, and contrary to the expert opinion tendered so long ago. He also asked him to look at the division that had taken place between the Western Infirmary and the Beatson Memorial Hospital, whereby the Western would have only 40 beds, and the Radium Centre about two miles away.

Mr. NIXON BROWNE replied that they thought the Regional Hospital Board was right in its latest decision. Mr. HANNAN is to raise the matter again.

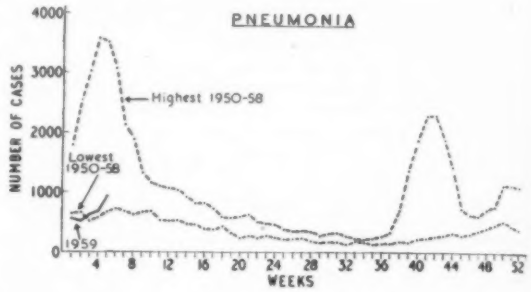
Helicopter Assistance

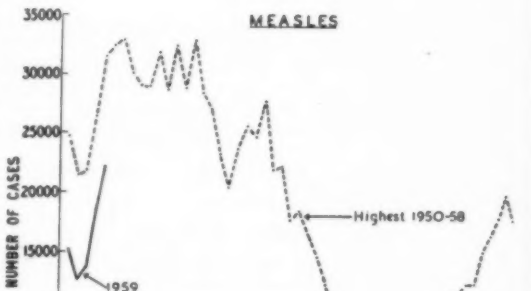
Mr. MICHAEL NOBLE (Argyll, Con.) asked the Secretary of State for a further statement about the air ambulance service. Mr. MACLAY said that improved helicopter cover would be provided by the Royal Navy and the Royal Air Force so long as they had helicopters in the area to meet their military requirements. The improvements affected the islands without scheduled airfields and remote areas on the mainland. It would be possible to use the helicopters to transport patients on a less restricted basis than at present.

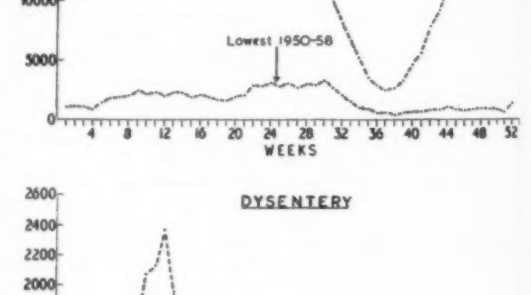
Vital Statistics

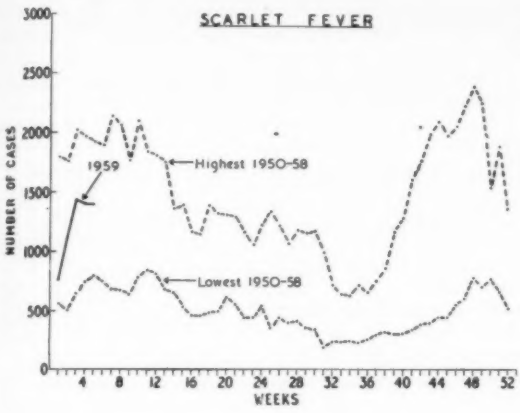
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ————. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending February 7

In England and Wales during the week ending February 7 the number of deaths from influenza was 144, an increase of 90 over the previous week's total. 41 were in Lancashire, 23 in Warwickshire (Birmingham C.B. 20), 10 in London, and 10 in Middlesex. The age distribution of the 144 influenza deaths was as follows: under 15 years, 2; 15–64 years, 59; 65 and over, 83. Pneumonia notifications numbered 943, compared with 679 in the previous week. Pneumonia deaths rose by 171, from 815 to 986. In the week ending February 3 new National Insurance claims numbered about 236,000, an increase of 28,000 over the figure for the previous week.

The largest rises in the notifications of other infectious diseases were 4,145 for measles, from 18,025 to 22,170, and 213 for dysentery, from 1,081 to 1,294; the largest falls were 101 for whooping-cough, from 859 to 758, and 28 for food-poisoning, from 157 to 129.

The largest rises in the incidence of measles were 621 in Essex, from 1,549 to 2,170 (Ilford M.B. 366, Hornchurch U.D. 236, West Ham C.B. 201); 397 in Warwickshire, from 699 to 1,096 (Birmingham C.B. 382, Coventry C.B. 343); 377 in Lancashire, from 1,801 to 2,178 (Manchester C.B. 242, Liverpool C.B. 217); 293 in Hampshire, from 331 to 624 (Southampton C.B. 168, Gosport M.B. 107); 283 in Yorkshire West Riding, from 1,828 to 2,111 (Leeds C.B. 346, Sheffield C.B. 289); 240 in Surrey, from 641 to 881; 204 in Durham, from 792 to 996 (Gateshead C.B. 151, Bishop Auckland U.D. 122); 200 in Staffordshire, from 445 to 645. 1,389 cases of scarlet fever were notified, being 7 fewer than in the preceding week; the largest fluctuations in the trends were a decrease of 56 in Lancashire, from 179 to 123, and a rise of 28 in Essex, from 82 to 110. Small falls in the incidence of whooping-cough were recorded in most areas, but the largest fluctuation was a rise of 26 in Yorkshire West Riding, from 61 to 87. 2 cases of diphtheria were notified, one more than last week, and both cases were notified in Birmingham C.B.

A further 3 cases of paratyphoid fever were notified in Lancashire, Whiston R.D., where 7 cases were notified in the preceding week.

The notifications of acute poliomyelitis numbered 18, and these were 8 fewer for paralytic and 5 more for non-paralytic cases than in the preceding week; the largest returns were Hampshire 5 (Southampton C.B. 5) and Yorkshire West Riding 4 (Leeds C.B. 3).

The largest rises in dysentery were 91 in Yorkshire West Riding and 90 in Lincolnshire. The chief centres during the week were Yorkshire West Riding 255 (Leeds C.B. 79, Bradford C.B. 59, Wakefield C.B. 43, Mexborough U.D. 42, Barnoldswick U.D. 13), Lincolnshire 155 (Grimsby C.B. 65, Scunthorpe M.B. 16), Glamorganshire 137 (Cardiff C.B. 65, Barry M.B. 43, Rhondda M.B. 19), London 92 (Islington 20, Wandsworth 20), Lancashire 78 (Manchester C.B. 23, Liverpool C.B. 15), Warwickshire 74 (Coventry C.B. 66).

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 31** (No. 4) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria ..	1	0	4	0	3	1	0	0	0	
Dysentery ..	1,081	114	171	17	19	829	62	133	10	1
Encephalitis, acute	2	1		0		2	0		0	
Enteric fever:										
Typhoid ..	1	0	1	0	1	2	0	0	0	
Paratyphoid ..	8	0	0	0	2(B)	1	0	0	0	
Food-poisoning ..	157	12	5	0		127	17	9	0	
Infective enteritis or diarrhoea under 2 years				11	29				13	12
Measles*	18,025	1302	362	237	850	2,338	39	67	34	2
Meningococcal infection	31	1	12	0	3	39	6	13	1	1
Ophthalmia neonatorum	19	5	5	0		25	0	6	0	
Pneumonia† ..	679	64	435	10	1	917	68	380	15	7
Poliomyelitis, acute:										
Paralytic ..	20	2	1	0	1	18	2	1	0	2
Non-paralytic ..	1	0	0			6	1			
Puerperal fever§ ..	199	34	13	1		204	32	12	4	
Scarlet fever ..	1,396	87	82	33	41	821	53	63	10	14
Tuberculosis:										
Respiratory ..	528	64	85	9		541	66	97	10	
Non-respiratory	56	4	10	6		58	4	14	6	
Whooping-cough	859	27	49	76	151	569	36	33	3	16

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria ..	0	0	0	0	1	No corresponding figures available.	0	0	0	0
Dysentery ..	0	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	1	0	1		0	0	1	1
Influenza	54	2	8	0	2		15	1	0	1
Measles		1	0	0	0		0	0	0	0
Meningococcal infection		1	1				0	0		
Pneumonia ..	815	81	64	21	14		98	34	15	15
Poliomyelitis, acute	1	0		0	0		0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	127	11	8	1	3		10	9	2	4
Non-respiratory		2	1	0	0		3	0	0	1
Whooping-cough	1	0	0	1	0		0	0	0	0
Deaths 0–1 year ..	394	35	29	8	17		35	32	10	18
Deaths (excluding stillbirths) ..	13,112	1101	861	152	245		1107	724	132	201
LIVE BIRTHS ..	14,515	1208	1069	241	408		1139	1009	223	341
STILLBIRTHS .	324	25	22				24	37		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Hunterian Festival.—The Royal College of Surgeons commemorated once again, with its biennial Hunterian Festival on February 16, surgery's debt to John Hunter. In the afternoon Sir REGINALD WATSON-JONES delivered, in the "Hunterian manner," the customary Oration. He had been instrumental in having *x* rays applied, not to bones, but to the Reynolds portrait of Hunter, and this has settled an age-old controversy. Under the present head is an earlier, younger-looking head of John Hunter, but not situated as some have supposed upside-down at the foot of the picture—a nice example of Hunterian method in an unusual field. The festival dinner, under the chairmanship of the President of the College, Sir JAMES PATERSON ROSS, attracted the attendance of no fewer than five Ministers of the Crown—six but for the 'flu—the French Ambassador, the High Commissioner for South Africa, leaders of industry, and many other distinguished guests. The Hunterian Festival is an occasion when, in the President's words, the College takes stock of its place in the world at large, and in his reply to Sir DAVID ECCLES's toast Sir JAMES dwelt on some of the College's achievements as a Commonwealth institution. The two Vice-presidents, Mr. A. DICKSON WRIGHT and Sir ARCHIBALD MCINDOE, proposed the healths, respectively, of "The Guests" and the Orator. The BISHOP OF LONDON replied for the guests.

The College announced on February 17 that Mr. J. COTTON, the property owner, is to give £100,000 to the College to establish a Chair in Biochemistry.

Hunterian Society.—Among the distinguished guests of the Hunterian Society at the annual dinner, held at the Savoy Hotel on February 12, were the MARQUESS OF EXETER, the LORD MAYOR OF LONDON, and LORD ADRIAN, O.M. Proposing the main toast, the MARQUESS OF EXETER described the Hunterian Society as a friendly, happy one—a family co-operation. The LORD MAYOR, Sir Harold Gillett, said that the City was doing its best to help the medical profession by abolishing smoke. LORD ADRIAN, replying for the guests, found comfort from the fact that a public address was something John Hunter could not take in his stride—he had to fortify himself with a draught of laudanum. Dr. FRANCIS LESLIE, the president of the Society, thanked all those who had made possible the successful meetings held during the year. The health of the Lord Mayor was proposed by Dr. CHARLES F. WHITE and that of the guests by Dr. G. B. MITCHELL-HEGGS.

Rockefeller Foundation.—In the last quarter of 1958, grants totalling over $8m. were awarded by the Rockefeller Foundation, more than half of which went to medical education and public health and biological and medical research. The principal grant to Britain during the quarter was $150,000 to the Medical Research Council; this continues, up to August, 1964, the Foundation's long-standing support of the Council's overseas fellowship programme. A grant of $28,500 was made to the Royal College of Physicians, London, to assist the Association for the Study of Medical Education in Great Britain during its developmental years. Sheffield University received $8,000 for research equipment in the department of biochemistry. Overseas grants of general interest include $500,000 to support the University of Chicago's new Section of Nuclear Medicine over a period of 10 years; this department will examine the legal, psychological, and social implications in community development and industry of problems arising from the use of nuclear energy. Eight Polish scientists and doctors share grants totalling over $25,000 for visits to various centres, mainly in the United States and Europe. Three are professors from Poznan, Cracow, and Warsaw, who are to observe developments in medical education. A small grant has been made to enable an American professor of psychiatry to visit Nova Scotia in connexion with a pilot study of possible special training in mental health for clergymen.

Ford Foundation—E.S.U. Travel Grant.—The English-Speaking Union invites applications from doctors in general practice (preferably in the 30's but not over 50) for a Ford Foundation—English-Speaking Union travel grant to visit the United States for 56 days, within the period mid-September, 1959, to June, 1960. The purpose of all grants under this scheme is to enable holders not only to learn what is being done in the United States in their own field but to travel widely and meet Americans in various walks of life. Further details and application forms are obtainable from the Secretary, The English-Speaking Union of the Commonwealth, Dartmouth House, 37, Charles Street, Berkeley Square, London, W.1. The closing date for applications is May 25.

Wellcome Trust Grant.—The vice-chancellor of Cambridge University has announced that the Wellcome Trust have offered to the university a grant not exceeding £120,000 towards the cost of adding a new wing to the department of biochemistry.

Royal College of Surgeons of England.—The following have been elected to an honorary fellowship of the College: Professor A. A. McConnell (Dublin), Mr. E. D. Ahern (Brisbane), Dr. J. H. Gibbon (Philadelphia), Dr. P. R. Hawley (Chicago), Dr. R. Lewisohn (New York), and Dame Lillian M. Penson (London).

University of Aberdeen.—Sir DAVID CAMPBELL, who was appointed Regius professor of materia medica 29 years ago, is to retire on September 30. Dr. A. G. MACGREGOR, senior lecturer in therapeutics at Edinburgh University, has been appointed to succeed him.

Royal College of Physicians, Ireland.—Dr. R. H. MICKS was elected King's professor of materia medica and pharmacy at a meeting of the college held on February 6.

Height and Weight Charts.—Height and weight charts for boys and girls can now be obtained, at 1½d. each plus postage, from the Medical Research Unit, National Spastics Society, Department of Child Health, Guy's Hospital, London, S.E.1. This type of chart, based on British standards, has not been generally available hitherto, and the present charts are constructed from data from the Oxford Child Health Survey and the London County Council reports on the heights and weights of school pupils in the County of London in 1954.

Ship-to-Shore.—The new Post Office ship-to-shore radio station at Hoare Down, Ilfracombe, was opened at the end of last month by the Assistant Postmaster-General, Mr. K. THOMPSON (*Western Morning News*). It supersedes the temporary station at Ilfracombe, and, with Stonehaven Radio, is the most modern installation of its kind in the country. In addition to the routine work of link-calls and telegrams, it monitors the two wavelengths used by shipping for distress calls. The station also operates a medical service for ships without a doctor, and is linked with the Ilfracombe Tyrrell Hospital.

"Scottish Medical Journal."—Dr. ALEXANDER BROWN, editor of the *Scottish Medical Journal*, has resigned. Dr. A. R. CURRIE, the assistant editor, is to succeed him.

Commonwealth Medical Advisory Bureau.—The Bureau has prepared a summary of regulations for postgraduate diplomas and courses of instruction in postgraduate medicine for the use of overseas educational authorities. Such authorities may obtain copies by writing to Dr. R. A. PALLISTER, Commonwealth Medical Advisory Bureau, B.M.A. House, Tavistock Square, London, W.C.1.

Overseas Medical Appointments.—A booklet describing the opportunities and conditions of medical work in the colonies has been issued this week by the Colonial Office. Copies may be obtained from the Director of Recruitment, Colonial Office, Great Smith Street, London, S.W.1.

Medical Electronics.—The council of the Institution of Electrical Engineers has instituted a medical electronics discussion group at which electrical engineers specializing in electronics can discuss matters of common interest with members of the medical profession. Details can be obtained from the Institution of Electrical Engineers, Savoy Place, London, W.C.2.

W.M.A.—At the annual meeting of the British Supporting Group for the World Medical Association, Dr. T. H. MANNERS KERFOOT was elected president for 1959 in succession to Dr. ALEXANDER HALL, a former president of the B.M.A. Dr. Kerfoot is also president of the Association of British Pharmaceutical Industry.

Liverpool University.—Dr. R. W. SMITHELLS has been appointed lecturer in child health.

Professor F. A. E. Crew, F.R.S., is to spend four months in Bombay as visiting professor of preventive and social medicine at Topiwala National Medical College under the auspices of W.H.O.

Professor G. Gordon Lennon, professor of obstetrics and gynaecology at Bristol University, has been elected an honorary member of the Turkish Society of Gynaecology.

COMING EVENTS

B.B.C. Television.—"Lifeline" programme on termination of pregnancy, February 26, 10.15–10.45 p.m.

Grey Turner Surgical Club.—Meeting at Cardiff, March 16–18. Details from Mr. G. N. BAILEY, F.R.C.S., 2a, Lancaster Road, Harrogate.

Mental Health Research Fund.—Annual meeting at 5 p.m., March 18, at 26, Portland Place, London, W.1.

Ergonomics Research Society.—Conference on "Ergonomics—Its Place in Industry," April 6–9, at Balliol College, Oxford. Details from Dr. S. GRIEW, Department of Psychology, 22, Berkeley Square, Bristol, 8.

Joint Meeting on Chest Diseases. — The British Tuberculosis Association and the Thoracic Society of Wales are holding a joint meeting in Cardiff on April 17 and 18. Details from the British Tuberculosis Association, 59, Portland Place, London, W.1.

Institute of Diseases of the Chest.—Week-end course for general practitioners, April 18 and 19. Details from the Dean of the Institute, Brompton, London, S.W.3.

International College of Surgeons.—British surgeons are invited to form a representative delegation to the following meetings of the International College: (1) European Meetings.—(*a*) German Section, June 1–3, in Hamburg; (*b*) French Section, June 19–21, in Lyons. (2) 24th Annual Congress, September 13–17, in Chicago. (3) 12th Biennial International Congress, May 15–18, 1960, in Rome. Further information may be obtained from Dr. J. F. BRAILSFORD (Treasurer and Secretary for the British Isles), 20, Highfield Road, Edgbaston, Birmingham, 15.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, February 23

HUNTERIAN SOCIETY.—At Mansion House, 8.30 p.m., Hunterian Society Oration by Sir Arthur Porritt: John Hunter's Women.

INSTITUT FRANÇAIS DU ROYAUME-UNI.—At Queensberry Place, South Kensington, S.W., 8.30 p.m., French Scientific Films.

MANCHESTER MEDICAL SOCIETY: (1) SECTION OF ODONTOLOGY.—At Lecture Room, Dental Hospital, 4.30 for 5 p.m., Mr. D. Lloyd Griffiths: Common Ground. (2) SECTION OF GENERAL PRACTICE.—At Large Anatomy Theatre, Manchester University, 8.30 for 9 p.m., Dr. R. Ollerenshaw: Medical Illustration—Development of a New Service.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Guest lecture by Dr. R. M. Marquis: Heart Disease in Pregnancy.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Professor A. Haddow, F.R.S.: Chemistry and Biology of Cancer—(3) Properties of the Cancer Cell—Experimental Chemotherapy.

Tuesday, February 24

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. T. A. J. Prankerd: Viability and Survival of Red Cells.

FOUNTAIN HOSPITAL.—5.30 p.m., subject: Kernicterus. Papers by Professor G. H. Lathe and Dr. P. E. Sylvester.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. G. Cochrane: Leprosy (II).

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professorial Unit Staff: Tests of Acoustic Function. I.

MANCHESTER MEDICAL SOCIETY.—At Large Anatomy Theatre, Manchester University, 4 for 4.30 p.m., University Lecture on the History of Medicine by Dr. K. D. Keele: Leonardo da Vinci as Biologist.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Brigadier R. E. Tunbridge: Diagnostic Problems in Disorders of the Biliary Tract.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. R. A. Goodbody: Repair.

ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At New Small Lecture Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., Mr. J. Wrigley: Development of National Health Service Statistics.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. George Pinker: Pudendal Nerve Block for Obstetrical Anaesthesia.

Wednesday, February 25

BRITISH PSYCHOLOGICAL SOCIETY.—At Medical Society of London, 8.30 p.m., Professor I. C. Kaufman (Boston): Some Psychological Factors in the Aetiology of Epilepsy.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Blood and Bone Marrow Changes in Reticulosis.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. C. Oswald: Pneumonia.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professorial Unit Staff: Tests of Acoustic Function. II.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. R. C. Higham: Transurethral Methods of Treatment.

OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Professor L. N. Pyrah: Some Aspects of Renal Calculus Formation.

Thursday, February 26

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. D. I. Williams: Non-Tuberculous Granulomas.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professorial Unit Staff: Tests of Vestibular Function. I.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., ordinary meeting. Dr. N. B. Jones and Dr. G. Ansell: Symposium on Cortisone.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., symposium by Dr. Geoffrey Konstam, Dr. J. N. Morris, and Professor John Yudkin: Coronary Thrombosis.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor C. Havard: Non-malignant Bile Duct Obstruction.

ROYAL NORTHERN HOSPITAL.—2.45 p.m., Dr. J. Luder: Some Recent Advances in Paediatrics.

ROYAL SOCIETY FOR THE PREVENTION OF ACCIDENTS: INDUSTRIAL SAFETY DIVISION.—At Royal Society of Arts, 6, John Adam Street, London, W.C., 2.30 p.m., Alexander Redgrave Memorial Lecture by Mr. R. E. Tugman: Responsibility of Management for the Prevention of Industrial Accidents.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Denis Williams: neurology.

Friday, February 27

HEBERDEN SOCIETY.—At Physiology Lecture Theatre, London Hospital, 5 p.m., clinical meeting. papers by Dr. R. M. Mason, Dr. R. D. Catterall Dr. W. G. Wenley, Dr. D. Greenbaum, Dr. V. L. Steinberg, and Mr. O. J. Vaughan-Jackson.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. D. I. Williams.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. N. C. Oswald.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professorial Unit Staff: Tests of Vestibular Function. II.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Guest lecture by Professor G. A. Smart: Auto-immune Reactions in Thyroid Disease.

●ROYAL INSTITUTION.—9 p.m., Woodhull Lecture by Professor C. H. Waddington, Sc.D., F.R.S.: Evolutionary Systems—Animal and Human.

Sunday, March 1

UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., meet in Front Hall of main Hospital. Lecture-demonstration for general practitioners. Clinical demonstration by Dr. C. J. Hodson: Recent Advances in Radiology.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Armson.—On February 1, 1959, the result of an accident, Charles James Armson, M.R.C.S., L.R.C.P., of Brook House, Yoxall, Burton-on-Trent, Staffs.

Evans.—On January 21, 1959, in a nursing-home, York, Alexander Evans, M.R.C.S., L.R.C.P., formerly of Market Weighton, Yorks, and Southampton, Hants, aged 82.

Gardner.—On January 27, 1959, at his home, 107, Arundel Avenue, Liverpool, George Sheridan Gardner, M.B., B.Ch.

MacGowan.—On January 29, 1959, at Skelton Manor, York, Thomas James Berry Arnott MacGowan, M.B., Ch.M., F.R.C.S.

McDonnell.—On January 22, 1959, Michael Francis McDonnell, M.B., B.Ch., D.P.H., of Hillside Drive, Gravesend, Kent.

McIntosh.—On February 1, 1959, in a nursing-home, Edinburgh, James Wilson McIntosh, M.B., F.R.C.S.Ed., of 15, Grange Road, Edinburgh, formerly of 15, Nelson Street, King's Lynn, Norfolk, aged 83.

McQueen.—On January 27, 1959, at his home, Lynwood, Rushbrooke, Co. Cork, Campbell McQueen, *M.C.*, L.R.C.P.&S.I., and L.M., M.Sc., Lieutenant-Colonel, R.A.M.C., retired.

Pryn.—On January 26, 1959, the result of an accident, Edward John Pryn, M.R.C.S., L.R.C.P., Colonel, late R.A.M.C., of Drury Lodge, Colchester, Essex.

Starkey.—On January 19, 1959, at The Close, Llanfairfechan, Caerns., William Starkey, M.B., B.Ch.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Preventing Foetal Abnormalities

Q.—*What measures, particularly dietary, may be taken in the antenatal period to prevent foetal abnormalities?*

A.—Animal experiments, mostly carried out on the rat, have shown that deficiency of any one of a number of vitamins may result in congenital anomalies in the young. These include vitamin A, riboflavin, pteroylglutamic acid (folic acid), pantothenic acid, and vitamin E. The type of defect produced is probably largely dependent on the precise time in pregnancy of the vitamin deficiency and its degree. Hydrocephalus and anencephaly have been particularly noted in pteroylglutamic acid deficiency.

There is no reliable evidence that vitamin deficiencies play a part in the production of congenital anomalies in the human foetus. To be comparable to the situation induced in the experimental animal, either considerable amounts of an anti-metabolite would have to be taken by the woman during early pregnancy or a very abnormal and restricted diet given. There is some evidence that the incidence of certain congenital deformities varies with social class and the season of the year. Anencephaly, for instance, may be more frequent in babies conceived in the early spring, and this could be explained as the result of vitamin A deficiency in the winter diet.

It needs to be emphasized, however, that the cause of many congenital anomalies has hardly passed out of the realms of speculation. There is no indication as yet for special vitamin therapy during pregnancy, which might, at least in theory, even be harmful in some instances. The most sound advice is that every woman, throughout the reproductive period of her life and not only during pregnancy, should have an ample well-balanced diet.

Dental Tartar

Q.—*Is there any diet or drug treatment to reduce salivary acidity leading to production of an excessive amount of tartar? Is excessive tartar injurious to the teeth?*

A.—There would seem to be little evidence to support the view that the formation of an excessive amount of tartar is associated with acidity of the saliva. The current view is that the formation of tartar is essentially a bacterial process in which colonies of micro-organisms and debris provide the matrix for a deposit of calcium salts from the saliva. Factors predisposing to deposition would be a viscid saliva, lack of friction, as when a tooth is unopposed, irregularity of teeth, or roughness of surface. Little is known about the probable constitutional factors which may also be involved.

Prevention depends, therefore, largely upon good oral hygiene, and, while diet and drug treatment prescribed to alter the *p*H of the saliva is unlikely to be successful, the finishing of a meal with fibrous food, such as celery or an apple, is a simple method of improving oral hygiene. Considerable damage to the supporting structures of the teeth results if tartar is not regularly removed. Tartar prevents the natural stimulation of the gum margin by the friction of food, and the gums become inflamed by the products of the micro-organisms which grow and multiply under the tartar. The result is a chronic inflammatory condition of the gingival margin which gradually spreads to the periodontal membrane and bone supporting the teeth. When this happens the condition is popularly known as pyorrhoea, which is responsible for the loss of more teeth than any other dental disease. It can, however, be arrested if not too advanced by scaling and careful attention to oral hygiene.

Frischzell Treatment in Mongolism

Q.—*In view of recent publicity on the fresh-cell treatment of mongolism, could you give some opinion on the results of such treatment and also upon the methods employed?*

A.—Mongolism is a congenital disorder of which the basic cause is quite unknown. All the distinguishing features are present at birth, even in the premature, and it is likely that the disordered development of tissues which results in the characteristic group of anomalies occurs very early in foetal life. The cardiac abnormality which is frequently associated with mongolism must be initiated in the 2nd–4th month of pregnancy. The failure of cerebral development and the disturbance of bone growth, which gives the typical mongolian appearance, probably occur a little later in foetal life.

There can be no question therefore of a cure for mongolism. It is not similar to those metabolic disorders, such as galactosaemia and phenylketonuria, in which the brain is normal at birth. In these conditions a suitable diet can prevent cerebral damage, if given soon after birth. Nor does it resemble cretinism, in which normal development may follow therapy with thyroid, except in one respect. Some mongols seem to suffer from mild thyroid deficiency and be slightly brighter and more lively when treated with thyroid. It follows that in prevention, once the cause is found, lies the only real hope of treatment; perhaps some form of therapy might be effective in early pregnancy. It is even possible that progressive cerebral failure might be halted by treatment soon after birth.

A condition such as mongolism, incurable by orthodox measures, bringing tragedy to many families and affecting particularly the more elderly mothers, is wide open to the quack. Furthermore, it is extremely easy in a mongol to obtain a subjective impression of improvement which is not necessarily apparent to the impartial observer. Phasic improvement and deterioration within small limits may be correlated with changes in general health or with periods of extra attention and care. It is easy to see how a firm belief can be founded in the value of a form of therapy put over with an impressive show of pseudo-science. Fresh cell (frischzell, sicca cell) therapy is claimed to be of value in a wide variety of conditions, including mongolism. It is possible, even if unlikely, that a carefully controlled trial might show it to have some value in some of these. It does not appear likely to be worth even a trial in mongolism, involving as it does the injection, as Professor Fanconi[1,2] notes, of foreign protein and unsterilized material.

REFERENCES
1 Fanconi, G., *Schweiz. med. Wschr.*, 1957, **87**, 1180.
2 —— quoted by Fasser, Ellis, *S. Afr. med. J.*, 1958, **32**, 672.

Correction.—We regret that we omitted the name of Major-General R. Murphy, C.B., C.B.E., from the list of those promoted to Commander in the Venerable Order of the Hospital of St. John of Jerusalem (*Journal*, February 7, p. 362).

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